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CONTENTS OF VOLUME XXII

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JULY, 1946. NUMBER 4

SEPTEMBER, 1946. NUMBER 5

NOVEMBER, 1946. NUMBER 6

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NECROTIZING ARTERIAL LESIONS RESEMBLING THOSE OF PERIARTERITIS NODOSA AND FOCAL VISCERAL NECROSIS FOLLOWING ADMINISTRATION OF SULFATHIAZOLE

REPORT OF A CASE *

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With the advent of the sulfonamides there came reports of many and varied clinical manifestations of toxicity and sensitivity that so often follow the introduction of a new drug. These various reactions have been reported in a voluminously growing literature,[1-3] and range in nature from mild febrile reactions [4] to marked skin sensitivity,[5] focal visceral necrosis, and, as most recently reported by Rich,[6-9] vascular lesions resembling periarteritis nodosa.

Hageman and Blake,[10] as early as 1937, recognized the possibility of reactions to the sulfonamides of an allergic nature and commented on the similarity of the clinical picture to the manifestations of serum sickness. In 1939, Erskine [11] suggested that this reaction might be mediated by the conjunction of sulfonamides with serum proteins, and, indeed, Schönholzer,[12] Wedum,[13] Davis,[14] and others subsequently demonstrated the linkage of sulfonamides to plasma protein in experimental studies. It appears that of all the sulfonamides in current use, sulfathiazole is perhaps the chief offender in this respect.

As for the anatomic expression of these untoward reactions, French and Weller,[15] in 1942, called attention to the rather frequent finding of interstitial myocardial lesions, rich in eosinophils, in subjects known to have received one or another of the sulfonamides within 30 days of their death. Similar focal lesions were also observed by them in the lung, liver, and kidney, and comparable lesions were reproduced in mice and rats. Shortly thereafter, Lederer and Rosenblatt [16] reported on their findings in 4 cases treated with sulfathiazole, in which numerous areas of focal necrosis were noted microscopically in practically all viscera. About the same time, Merkel and Crawford [17] reported 4 cases with similar lesions in which sulfathiazole was also implicated.

Rich,[6,7] in 1942, observed vascular lesions resembling periarteritis

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nodosa in two subjects who had been treated with sulfathiazole. Since then, he has seen a number of similar cases.[18] These vascular lesions were associated with the presence also of widespread focal necrosis such as Lederer and Rosenblatt [16] and others had previously described. The vascular lesions were not unlike those Rich had observed in fatal cases of serum sickness, and he considered them to have developed on the basis of hypersensitivity reactions. Duff,[19] Black-Schaffer,[2] and Moore [20] have likewise observed arterial lesions in autopsied subjects who had received sulfonamides. Murphy, Kuzma, Polley, and Grill [21] also noted similar lesions in the kidney in cases with predominantly renal involvement.

Rich [9] has recently commented on the possibility that hypersensitivity to chemicals other than sulfonamides may also result in vascular lesions. He specifically cited an autopsy in which lesions resembling those of periarteritis nodosa appeared in a patient who had exhibited manifestations of hypersensitivity to iodine, which was administered for hyperthyroidism. In this connection, we might mention that we have also observed necrotizing arterial lesions, in association with a purpuric skin eruption, in a subject who had received moderate doses of phenobarbital over a prolonged period. It is of interest to note, furthermore, that Marine and Baumann [22] have recently described vascular lesions like those of periarteritis nodosa in 3 of 100 or more rats which had been fed thiouracil.

As for the sulfonamides, in general most of the sensitivity phenomena have followed their oral administration, their topical application, or their administration by the parenteral route. It has been recognized that similar sensitivity reactions can occur also after the local introduction of the sulfonamides into clean surgical wounds; but, to our knowledge, no fatal reactions have been described under these circumstances. We had occasion recently to observe a case in which the patient showed evidences of sensitivity reaction to sulfathiazole which had been introduced into a clean surgical wound but in which, despite this reaction, sulfathiazole was subsequently given by mouth, on the assumption that the wound had become infected. This patient died and was autopsied. It is of considerable interest that one of the manifestations of hypersensitivity was the presence of widespread vascular lesions resembling those of periarteritis nodosa, lesions such as Rich [6-9] has described.

Report of Case

Clinical History. The patient was an obese Negress, 61 years of age, who had had an open reduction for a subcoracoid dislocation of the right shoulder of 4 months' duration. Prior to closure of the wound, sulfathiazole was dusted into it, the amount thus introduced being 5 gm. or less. As far as is known, the patient had been in

good health prior to her injury and had had neither hypertension nor renal disease.

The postoperative course until the ninth day was uneventful. Then the patient had a chill, with an elevation of temperature to 103° F. At this time, it was noted that a vesicular skin eruption was present, small lesions being scattered over the trunk and extremities. The patient stated that these had been present for several days.

The wound was examined, but no evidence of infection was found. Cultures were taken of the wound, the vesicular skin lesions, and the blood. These remained sterile. Meanwhile, the patient was started on sulfathiazole, 1 gm. every 4 hours, on the premise that she had a wound infection, possibly associated with septicemia. Sulfathiazole was administered for 6 days, when it was discontinued at the advice of the dermatologic consultant, but not until the patient had received 31.5 gm. Penicillin was substituted without apparent benefit. After a few days, it was suspected that the patient's difficulty might be due to sulfathiazole reaction rather than infection, but by this time irreparable renal damage had been done, as evidenced by albuminuria, red blood cells in the urine, oliguria, steadily increasing azotemia (the nonprotein nitrogen mounting to 207 mg.), manifestations of acidosis, and finally the full syndrome of uremia. It is interesting to note, also, that the free cholesterol of the serum was as high as 75 per cent, indicating severe hepatic damage, and that the serum bilirubin was increased fivefold, suggesting increased destruction of red blood cells. The patient expired about 3 weeks after the operative intervention.

Post-Mortem Examination

The body was that of a large, obese, elderly Negress in rigor mortis. There was a recent surgical incision, approximately 10 inches in length, over the anterolateral aspect of the right shoulder and upper arm. It was partly closed by skin sutures and appeared to be healing. The shoulder and upper arm region appeared edematous and presented a brawny induration, but no evidence of infection. The skin presented clusters of dried, encrusted papules (apparently representing a healing stage of the vesicular lesions noted clinically). In addition, the skin also showed some evidence of scaling, but no hemorrhagic or bullous lesions were observed. The conjunctivae were intensely congested, and on the right showed edema as well. There was no peripheral edema, jaundice, or enlargement of the superficial lymph nodes.

The panniculus adiposus measured as much as 6 cm. in thickness, the fat being bright yellow. The peritoneal surfaces were smooth and glistening. There was a small quantity of cloudy yellowish fluid in both pleural cavities. The visceral pleura, especially over the lower lobes, appeared dull and in places was coated by fresh fibrinous exudate. Smear of this fibrin revealed the presence of pus cells, but no bacteria were found. The corresponding pulmonary parenchyma was firm and section revealed a patchy bronchopneumonia. The cut surfaces of the lungs, otherwise, were dark red and congested. The trachea and bronchi were filled with pinkish froth. There was no gross evidence of tuberculosis in the lungs or hilar lymph nodes.

The parietal and visceral layers of the pericardium were adherent. The heart was slightly enlarged in consequence of dilatation of its chambers. The myocardium was soft and yellow-brown. The valves showed no evidence of endocarditis. The coronary arteries and their branches appeared somewhat thickened, but were nowhere narrowed or occluded.

The liver was slightly enlarged, rather firm, pale, and presented a finely granular surface in places. The lobular architecture on section was not clearly outlined. The gallbladder was filled with numerous, small, faceted whitish stones, which on section presented the structure of mixed cholesterol-pigment gallstones.

The spleen was somewhat enlarged, but did not extend below the costal cage. The splenic pulp was very soft, although not diffluent, and the gray pulp was very prominent.

The adrenal glands presented nothing remarkable.

The pancreas was rather large, pale gray-yellow, and unusually firm.

The kidneys, embedded in a large mass of congested and indurated perirenal fat, were soft and friable. The cortical surfaces were relatively smooth, and showed no apparent hemorrhagic lesions grossly. On section, the kidneys presented evidence of severe parenchymatous degeneration. The glomeruli stood out as unusually prominent grayish flecks. There were no hemorrhages noted in the renal pelves, nor was any gravel or crystalline material observed in them. The ureters were not unusual. The urinary bladder was slightly dilated and presented a small diverticular out-pouching on its posterior wall. No concretions were found in the bladder, and the mucosa presented nothing remarkable, except for a single petechial hemorrhage.

Examination of the genital tract revealed atresia of the cervical canal, thick, yellow-brown, pus-like fluid in the endometrial cavity, and a slightly dilated and sealed right fallopian tube.

Examination of the gastrointestinal tract revealed nothing noteworthy. The mesenteric lymph nodes were not appreciably enlarged.

We were not permitted to examine the brain and spinal cord.

Portions of two ribs, a slice of the body of the sternum, and part of the 4th lumbar vertebral body were taken for routine histologic examination.

Microscopic Examination

Microscopic sections revealed rather unusual lesions which had not been anticipated from the gross findings. These were essentially of two types: first, focal necrosis in the liver, lung, myocardium, spleen, gallbladder, and pancreas; and second, necrotizing arterial lesions like those of periarteritis nodosa in the kidneys, liver, spleen, gallbladder, adrenal glands, uterus, fallopian tubes, and elsewhere.

The focal visceral lesions, as noted, were widespread. They consisted essentially of rather small and fairly localized collections of inflammatory cells, associated with necrosis at the site of the lesion. The inflammatory cells were small mononuclear cells and polymorphonuclear leukocytes, including some that appeared to be eosinophils. These necrotic foci were most numerous in the heart (Fig. 7) and pancreas (Fig. 9), but could be found readily in many other viscera. In the liver (Figs. 5 and 6), for instance, numerous foci were observed both in the lobules and within periportal fields, where some of them had apparently broken into the lumina of radicles of the portal vein.

The vascular lesions also had a wide distribution (Figs. 1 to 5). They found their fullest expression in the kidneys (Figs. 1 to 3), but they were occasionally encountered in the spleen and gallbladder and, as noted, there was a scattering of them also in many other viscera. For the most part, it was the smaller arteries and arterioles that were affected, which perhaps would explain why none of the lesions were detectable grossly. Furthermore, virtually all of the lesions appeared to be fresh or acute, which is in keeping with the brief duration of illness in this case. Characteristically, there was observed at the site of these vascular lesions more or less complete fibrinoid necrosis of the wall of the artery, including its media. In hematoxylin and eosin preparations this was reflected by a homogeneous, bright eosin-staining, smudgy appearance. In many of the arterial lesions streaks of the same fibrin-like material extended into the perivascular exudate. The necrotic wall was infiltrated in places by polymorphonuclear leukocytes. Radiating out from the wall of the vessel were oval or spindle-shaped cells apparently of histiocytic nature. Interspersed with and surrounding these cells there was a perivascular inflammatory exudate of pleomorphic nature, including lymphocytes, plasma cells, mononuclear macrophages, and numerous polymorphonuclear leukocytes including some eosinophils. In some of the affected arteries the endothelial lining cells were found to be unusually large and swollen. In general, the appearance of these necrotizing arterial lesions was such that we could not distinguish them from the classical lesions of periarteritis nodosa.

Anatomical Diagnoses. Status (3 weeks) after open reduction of (4 months' old) subcoracoid dislocation of right shoulder, and the administration of sulfathiazole: necrotizing arterial lesions resembling those of periarteritis nodosa in kidneys, liver, spleen, gallbladder, adrenal glands, uterus, and fallopian tube (developing apparently on the basis of hypersensitivity to sulfathiazole); widespread foci of visceral necrosis; terminal azotemia; acute fibrinous pleuritis and patchy bronchopneumonia (bilateral); brawny induration of extracapsular soft tissues of right shoulder region; severe secondary anemia (hemato-

logically); severe parenchymatous degeneration of kidneys; enlargement of spleen; chronic cholecystitis and cholelithiasis; old pericardial adhesions; pleural adhesions (left); scarring of media of aorta (probably on old luetic basis); obesity.

Summary and Conclusions

A description is given of the changes observed at autopsy in a case of what appeared to be hypersensitivity to sulfathiazole, which had been introduced into a clean surgical wound made in the course of an open reduction of a subcoracoid dislocation. On the ninth postoperative day, the subject developed a chill, elevation of temperature to 103° F., and a vesicular skin eruption. The significance of these manifestations of sulfonamide hypersensitivity was not appreciated, and sulfathiazole was again administered on the mistaken premise that there was a wound infection, possibly associated with septicemia. The subject died about 3 weeks after the operative intervention with manifestations of uremia, evidence of severe hepatic damage, and also hyperbilirubinemia. The significant pathologic changes were the following: (1) necrotizing arterial lesions resembling those of periarteritis nodosa in the kidneys, liver, spleen, gallbladder, adrenal glands, uterus, and fallopian tube; (2) focal visceral necrosis in the myocardium, liver, lungs, spleen, gallbladder, pancreas, and elsewhere; (3) severe parenchymatous degeneration of the liver and kidneys; (4) acute fibrinous pleuritis and patchy bronchopneumonia (bilateral).

The changes found in this case have been discussed in relation to those in comparable cases in the literature. This case appears to be the first recorded instance of a fatal hypersensitivity reaction in which the initial sensitization was brought about by the introduction of sulfonamide into a clean surgical wound.

Failure to recognize the clinical manifestations of hypersensitivity to the sulfonamides (fever, chill, a skin eruption of hemorrhagic, vesicular, or bullous character, and failing renal function on or shortly after the seventh day following the administration of sulfonamides) may have serious consequences. Sometimes, as in the case presented, these manifestations may be misinterpreted as indications of infection calling for the administration of sulfonamides with renewed vigor, the effect of which may be likened to pouring gasoline on a fire.

Because sulfathiazole appears to be the principal offender in respect to hypersensitivity reactions, the indiscriminate use of this drug for minor infections or for prophylaxis seems ill advised. For enteral or parenteral use, sulfadiazine, for instance, is preferable, and for wound implantation, sulfanilamide.

Attention is directed to the fact that the administration of chemicals other than the sulfonamides (*e.g.*, iodine, phenobarbital, and thiouracil) also may be followed occasionally by the appearance of periarteritis nodosa-like lesions.

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[*Illustrations follow*]

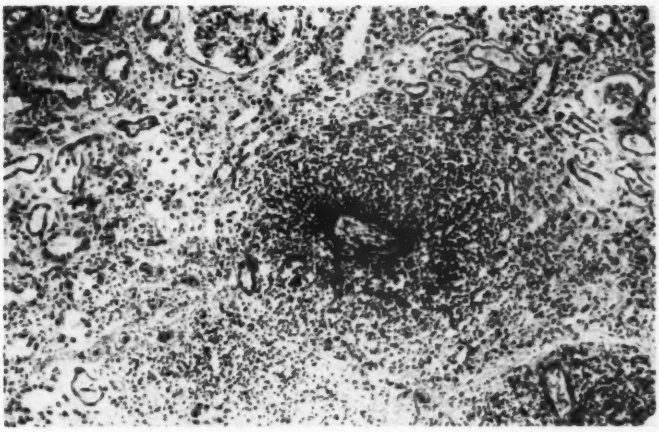
DESCRIPTION OF PLATES

PLATE 128

FIG. 1. A representative field of the kidney. In the center of the field there is a necrotic artery surrounded by a collar of inflammatory cells. In the lower right corner there is another perivascular collection of cells about a small artery, which in part is still preserved. The tubules are spread apart by edema, and the interstitial connective tissue is infiltrated by inflammatory cells. × 65.

FIG. 2. Higher magnification of the renal artery illustrated in Figure 1. The entire wall of the artery, including its media, is necrotic and in hematoxylin and eosin stain gave a homogeneous bright red, fibrinoid appearance. Streaks of this fibrin-like material extend out into the perivascular zone. Surrounding the arterial wall is a mantle of histiocytes or monocytes, and beyond this a zone of closely packed inflammatory cells may be seen, including mononuclear macrophages, lymphocytes, plasma cells, and polymorphonuclear leukocytes. Some of the leukocytes appeared to be eosinophils. ×200.

FIG. 3. Another interlobular artery in the kidney. There is fibrinoid necrosis and infiltration of the wall of the vessel by polymorphonuclear leukocytes. Radiating out from the necrotic arterial wall are oval or spindle-shaped histiocytic cells. × 375.



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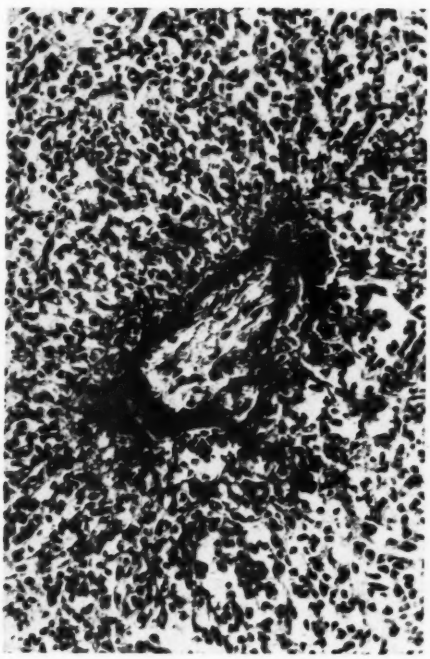

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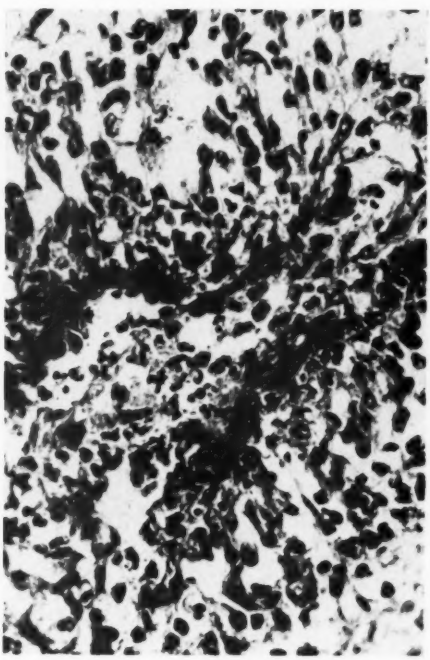

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Lichtenstein and Fox

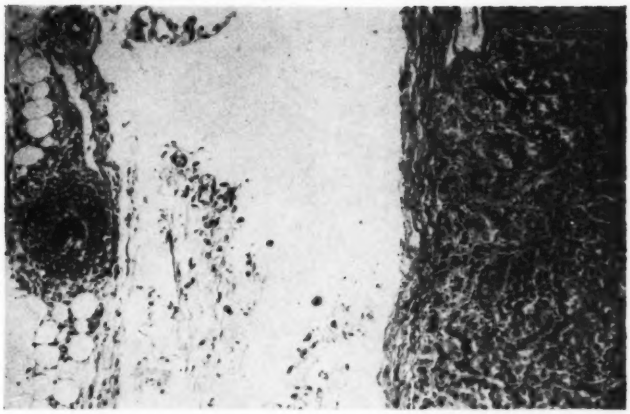
Arterial Lesions Following Sulfathiazole

PLATE 129

FIG. 4. A necrotic small artery in the fatty tissue around the adrenal gland. × 65.

FIG. 5. A periportal field in the liver. Below the center there is an affected arterial branch surrounded by a zone of inflammatory cells. There are also collections of inflammatory cells elsewhere in the periportal field. With hematoxylin and eosin stain one could observe fibrinoid necrosis of the vessel wall, and also that an appreciable number of the leukocytes were eosinophils. × 75.

FIG. 6. A focus of necrosis and cellular infiltration within a liver lobule. The inflammatory cells are of varied character and represent lymphocytes, plasma cells, mononuclear macrophages, and polymorphonuclear leukocytes, including a considerable number of eosinophils. ×350.



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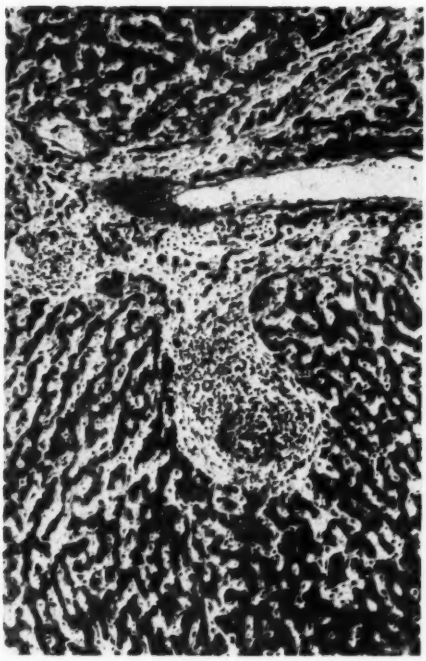

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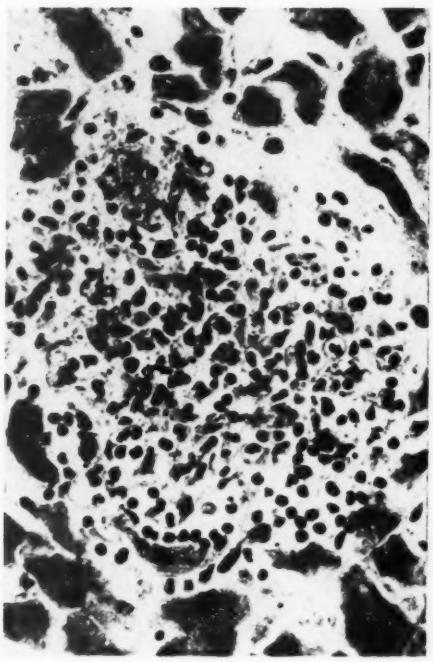

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Lichtenstein and Fox Arterial Lesions Following Sulfathiazole

PLATE 130

FIG. 7. Focal necrosis within the myocardium. At higher magnification it was evident that a majority of the inflammatory cells were polymorphonuclear leukocytes. × 250.

FIG. 8. A field in the lung. The dark-staining material within the alveolar walls and alveolar spaces resembles fibrin in the hematoxylin and eosin preparation, and is interspersed with macrophages and polymorphonuclear leukocytes. × 200.

FIG. 9. A representative field in the pancreas. In the center of the field there is a small roundish focus of necrosis and cellular infiltration. At higher magnification it was observed that most of the cells within this focus were polymorphonuclear leukocytes. × 200.

FIG. 10. Sulfa-crystals within a renal tubule. There were comparatively few such crystal present. The more fully calcified masses no longer retained this characteristic structure. × 850.

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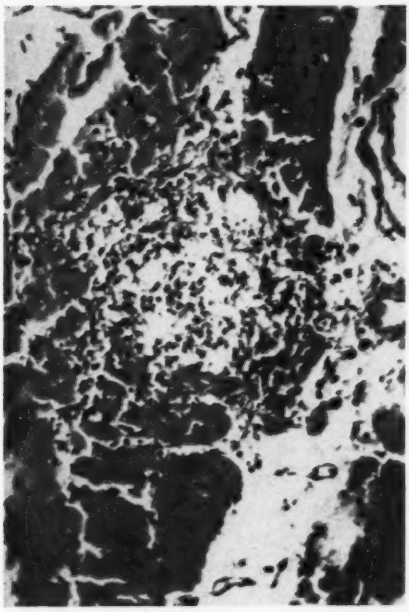

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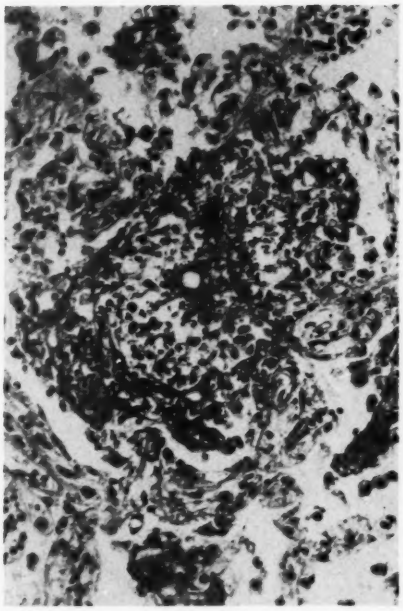

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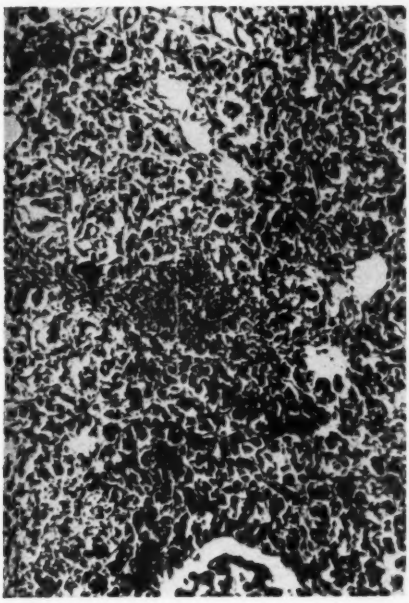

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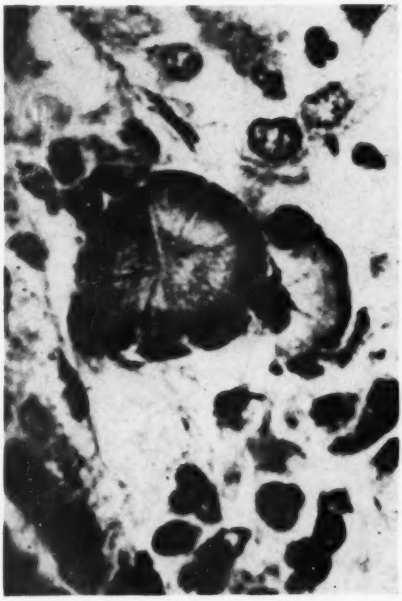

Lichtenstein and Fox

Arterial Lesions Following Sulfathiazole

HYPERSENSITIVITY IN THE PATHOGENESIS OF THE HISTOPATHOLOGIC CHANGES ASSOCIATED WITH SULFONAMIDE CHEMOTHERAPY *

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An earlier report on the effects of the sulfonamide drugs in tissues was published in collaboration with C. V. Weller in 1942.[1] At that time few reports of this character had been released, but subsequently there has been an increasing number in the literature. As each new sulfonamide derivative was introduced, the hope that it would prove to be less toxic than preceding ones was revived; however, after it had been used for a time, investigation proved that comparable tissue changes took place in one or several organs of the body.

The material utilized in this report includes 76 fatal cases investigated at the Army Institute of Pathology from 1937, when neoprontosil was first used therapeutically in Army hospitals, until 1943, when a variety of sulfonamides were being employed.

Skin taken for biopsy from 2 other cases was included in the material, making a total of 78 cases. This series is approximately one-sixth of more than 500 cases in which one or another type of lesion had resulted from the administration of sulfonamides, but complicating disease factors caused the other cases to be eliminated. All cases were excluded in which sulfonamide drugs had been given in the treatment of any of the following conditions: septicemia, confirmed by blood culture; rheumatic fever; cardiovascular disease, including coronary thrombosis; poliomyelitis; scrub typhus or other proved viral or rickettsial infection; trichinosis; diphtheria; scarlet fever; typhoid fever; or miliary tuberculosis. However, in the presence of many of these complicating diseases, cellular infiltrates were observed which were identical with those regarded as the characteristic sulfonamide effect.

The sulfonamide drugs which had been administered to the patients in this series included neoprontosil, sulfanilamide, sulfathiazole, sulfapyridine, sulfaguanidine, sulfadiazine, and the sodium salts of sulfathiazole, sulfapyridine, and sulfadiazine. Various combinations of these drugs were given to 24 patients. In four instances "sulfonamide therapy" was reported without reference to the specific drug employed (Table I).

The total dosage of sulfonamide drugs received by the patients during the terminal illness varied from 8 to 340 gm., over periods ranging

* Received for publication, September 30, 1945.

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from several days to 6 weeks. No case was included in the series in which death occurred later than 1 month after cessation of sulfonamide therapy. In all but 2 cases chemotherapy had been instituted at least 72 hours before death, but in these the drug had been given intravenously in moderately high dosage.

Clinical Data. Sulfonamide drugs were administered to 30 patients who were admitted to the hospital with a diagnosis of nasopharyngitis. Lobar pneumonia due to type I pneumococcus developed in 3 of these cases, due to type III pneumococcus in one, and in the remaining 26 there was terminal bronchopneumonia. Eleven of the 76 patients were being treated for gonorrhea and the remaining 35 for a variety of clinical conditions including fracture, perforated appendix, duodenal ulcer, and otitis media.

TABLE I

Sulfonamide Drugs Administered to Patients Included in the Reported Series *

Drug	No. of cases
Neoprontosil	1
Sulfanilamide	6
Sulfathiazole	22
Na sulfathiazole	3
Sulfapyridine	1
Na sulfapyridine	1
Sulfadiazine	11
Na sulfadiazine	4
Sulfaguanidine	1
Combinations	24
"Sulfonamide therapy"	4

* Two biopsy cases included.

Induced Sensitivity. In approximately one-half of the cases reported in this series there was clinical evidence of some reaction denoting sensitivity to the sulfonamide drugs. Table II lists these clinical complications which suggested sensitivity.

In 14 cases, more than one course of treatment with sulfonamides had been resorted to during the terminal illness of the patient. The first therapeutic course did not produce severe complications in all cases; apparently, in some the degree of sensitivity increased with repeated courses of the drugs. Rash, fever, chills, nausea, vomiting, cyanosis, or leukopenia were the usual signs of unfavorable reaction with the first course of sulfonamide therapy; hypoplastic anemia, icterus, anuria, dermatitis, or combinations of such grave complications, with a subsequent course of treatment. The exact length of treatment was not stated in the brief clinical summaries submitted with the protocols in most instances, so that the relationship of duration of therapy to clinical complication could not be calculated. Patients with hypoplastic or hemolytic anemia, dermatitis or anuria died following varying periods of therapy, but no definite relationship between induced sensitivity and duration of therapy, dosage, or a specific sulfonamide drug was apparent in cases completely reported. Multiple courses of sulfonamide therapy separated by intervals varying from hours to weeks appeared to result in acquired sensitivity.

Histopathology

Histopathologic lesions were found most frequently in the heart, liver, and kidney. Sections of intestine, gallbladder, urinary bladder, prostate, testis, lymph node, bone marrow, skin, skeletal muscle, and meninges were only occasionally represented in the material examined so that the corrected incidence of pathologic changes in these organs probably would be somewhat higher. The normal cellularity of organs such as the spleen, lymph nodes, and bone marrow contributed to the difficulty of establishing an increase in cell content, but the acidophilic cellular reactions to the sulfonamide drugs were obvious in these organs.

Table II

Clinical Complications in the Reported Cases Associated with the Administration of Sulfonamide Drugs

Clinical complications	No. of cases
Dermatitis	19
Anuria	9
Icterus	8
Aplastic anemia	7
Fever and/or chill	6
Eosinophilia in peripheral blood	2
Hemolytic anemia	2
Leukopenia	2

Heart

The heart lesions indicative of sulfonamide intoxication were those described by French and Weller [1] in experimental and clinical material and confirmed by Frist [2] and Flynn.[3] The characteristic cell found in the lesions in the heart and in all other organs examined was the acidophilic histiocyte. This cell, with variable numbers of other mononuclear and polymorphonuclear cells, both acidophilic and neutrophilic, was present in paravascular foci, or diffusely distributed between the cardiac muscle fibers, in the subepicardial areolar tissues, and beneath the endocardium. Necrosis was neither constant nor prominent in the tissues in which these cellular infiltrates were found, but did occur in the more severe cases (Figs. 1 and 2).

Distinctive vascular involvement (Figs. 3 and 4), such as that described by Rich [4] and confirmed in a personal review of this material by him, was noted in many of the hearts examined. In 16 cases vascular lesions were seen in organs other than the heart. The lesions consisted of endothelial edema and proliferation, fibrinoid necrosis of the vessel wall, and endarteritis and periarteritis with acidophilic histiocytes and eosinophils predominating in the inflammatory cellular reaction. The infiltrate in older lesions contained fewer eosinophils and relatively more histiocytes.

In addition to the inflammatory cellular reaction, epicardial, myocardial, or subendocardial hemorrhages, petechial or diffuse in character, were seen in the sections. Characteristic cellular infiltrates were

present throughout the walls of capillaries and venules adjacent to or in the hemorrhagic areas. In a few instances early fibroblastic proliferation was associated with inflammatory infiltrates; however, experimental reproduction of this change will be required before its significance in relation to the sulfonamide drugs can be evaluated.

Extensive focal calcification of the myocardium was observed in one case and calcification of isolated muscle fibrils in another; in neither was there evidence of vascular occlusion or other cardiac disease. A minimal acidophilic cellular infiltration in the adjacent myocardium was attributed to the sulfonamide drugs (Fig. 5). The significance of calcification of the myocardium was not apparent and its interpretation must await further experimentation. Calcification of the myocardium in rats fed sulfonamides, as reported by Endicott, Kornberg, and Daft,[5] may be a comparable lesion.

Liver

Lesions in the liver believed to result from the administration of sulfonamide drugs included infiltrations containing acidophilic histiocytes and neutrophils with varying degrees of focal necrosis or micro-abscess formation (Fig. 6). The presence of dense cellular infiltrations containing characteristic acidophilic cells, in the absence of other known cause for such collections of inflammatory cells (*i.e.*, cholelithiasis, choledocholithiasis, or other detectable biliary tract disease) was interpreted as evidence of reaction to sulfonamide drugs during the terminal illness.

In the liver as in the heart there was a minor degree of cellular infiltration in the wall of an occasional central vein. Hemorrhage was not noted in the liver.

Kidney

Renal lesions of many kinds were encountered in approximately one-half of the cases reviewed. Those believed to have been caused by the action of sulfonamides included ***interstitial nephritis,*** in which characteristic acidophilic mononuclear and polymorphonuclear cells were conspicuous components (Fig. 7); crystal formation (Fig. 8), often associated with calcium deposition, or with accumulations of bluish staining material both intratubularly and extratubularly; and vascular fibrinoid necrosis, thrombosis, subpelvic hemorrhages, and cellular infiltrates. Both focal necrosis and cellular infiltrates were seen in sections showing interstitial nephritis.

Tubular lesions were for the most part limited to the distal portions of the nephron, including the ascending limb of Henle's loop and the distal convoluted and collecting tubules, in which necrosis of the tubu-

lar epithelium and regeneration of the lining cells were seen. The lumina were plugged and the tubules distended with hemoglobin casts, crystals, crystals combined with calcium salts, erythrocytes, leukocytes, and amorphous protein precipitates. Some tubules showed necrosis of the lining with rupture of the walls and escape of crystals into the adjacent interstitial tissues. Glomerular and proximal tubular lesions were less frequent but glomerular vascular lesions were striking when present.

Subpelvic hemorrhages were conspicuous if ureteral and pelvic catheterization had been employed before death in an attempt to remove sulfonamide crystals. Hemorrhages and characteristic cellular infiltrates beneath the pelvic epithelium were also seen when there had been no surgical intervention. As in the heart, these hemorrhages and infiltrates were believed to be attributable to the sulfonamide drugs.

Skin

Sections of skin were included in only 2 of the fatal cases and were submitted for biopsy in 2 others. Inasmuch as a rash was reported in 18 cases, the skin changes must be regarded as significant. In the 4 specimens examined the characteristic acidophilic cells were present. The lesions, both clinically and histopathologically, were like those seen in erythema multiforme with vesiculation (Fig. 9) and in erythema nodosum (Fig. 10). The cellular infiltrates were mainly paravascular with some diffusion of cells in the more severe cases. Vascular involvement was not a salient feature.

Testis

Acidophilic histiocytes were striking in the sections of testis included in 4 cases in the series (Fig. 11). Because testicular tissue was submitted in so few cases, the true incidence of lesions in the testes could only be estimated. Although the acidophilic histiocytes were distributed in the supporting tissues of the testis, there was no possibility of confusion with Leydig cells. No necrosis or hemorrhage was present in the sections of testis examined.

Spleen, Lymph Nodes, and Bone Marrow

Specimens of spleen were received in 64 of the 76 cases studied. In 7, miliary foci of necrosis, similar to those reported by Lederer and Rosenblatt,[6] and Merkel and Crawford,[7] were encountered in the red pulp. These foci of necrosis were associated with acidophilic histiocytes and neutrophilic leukocytes (Fig. 12).

Lymph node lesions were present in 3 cases. As in the spleen and

bone marrow, microscopic foci of necrosis were seen in association with acidophilic histiocytes, granular leukocytes, and hyperplastic reticulum cells (Fig. 13).

Bone marrow changes were present in 5 cases in the form of miliary areas of focal necrosis and infiltrations of acidophilic histiocytes and polymorphonuclear cells.

Lung

Pulmonary lesions were the most difficult to interpret because of the bacterial inflammatory reaction usually present. However, in 4 instances definite intra-alveolar and interalveolar, peribronchiolar, peribronchial, and perivascular infiltrations of acidophilic histiocytes and polymorphonuclear cells were present. Vascular fibrinoid necrosis, capillary thrombosis, fibrinoid plaques in the alveoli, and interstitial cellular foci were noted in the lungs in addition to hemorrhage.

In 2 cases with acidophilic cellular infiltrate, massive pulmonary hemorrhage by diapedesis was present. In one case miliary necrotic foci were present in the lungs as well as in the liver, spleen, lymph nodes, and bone marrow. As already stated, any case in which there was miliary tuberculosis, tularemia, typhoid fever, or other known cause of focal necrosis was excluded from the series.

Other Organs

Foci of eosinophilic histiocytes have been found in practically all organs of the body, including all parts of the gastrointestinal tract, gallbladder (Fig. 14), urinary bladder, skeletal muscle, and meninges. Tissue from these organs was not routinely submitted in the 76 cases reported and, as a result, the lesions were encountered too infrequently to be significant statistically. They are important in that they showed the characteristic cellular infiltrates.

Discussion

Histopathologic changes in the kidneys have received more attention in the literature than those of other organs. As noted by Prien, Crabtree, and Frondel,[8] Climenko and Wright,[9] Antopol, Lehr, Churg, and Sprinz,[10] and Hellwig and Reed,[11] renal tubular damage was usually confined to the distal portion of the nephron, particularly the distal convoluted and collecting tubules. Hemoglobin casts were an outstanding feature in many instances and were indistinguishable, unless associated with crystals of acetylated sulfonamides, from the hemoglobin-laden tubules seen following transfusion incompatibility, hepatitis, blast or crush injury, or death from burns. Interstitial cellular infiltrations,

containing acidophilic histiocytes and neutrophils, and subpelvic hemorrhages were components of the renal lesions noted in cases receiving the sulfonamide drugs.

It is remarkable that so little significance has been attached to the possible clinical effect of the sulfonamide drugs on the heart. Except for the reference of Scheinberg and Ingle [12] to myocardosis in a patient who recovered following treatment with sulfanilamide, no direct reference to the effects of the drugs on the heart was found in the literature surveyed.

Conclusive evidence of a chronic effect of sulfonamide therapy has not been obtained experimentally, but focal calcification and minor degrees of early fibroblastic proliferation have been noted in association with cellular infiltrates. In one case of periarteritis nodosa, secondary cellular infiltration attributable to sulfonamide drugs appeared comparable to that described in Rich's [4] report. Dense cellular infiltrations, hemorrhages, and focal necrosis might be expected to result in at least minor degrees of fibrosis. The focal myocardial calcification noted in 2 cases in the series may be regarded as a more permanent effect of the drug than the cellular infiltration and may be an example in human material of the lesions noted in rats fed sulfonamide by Endicott, Kornberg, and Daft.[5]

Hepatic infiltration and necrosis, with or without icterus, were frequent findings. When combined with lesions of the heart, kidneys, skin, and blood-forming organs, the fatal termination can be attributed to the severity of the total reaction.

The extensive pulmonary hemorrhages in 2 cases were comparable to hemorrhagic lesions encountered in the heart and kidney. The possibility of a relationship between hemorrhage by diapedesis and sensitivity to sulfonamide drugs must await further experimental confirmation. However, Pinkerton [13] and Gessler [14] have reported similar cases related to sulfonamide therapy.

Skin sections were taken in 4 instances of frank dermatitis. These 3 cases of erythema multiforme with vesiculation and one of erythema nodosum were striking. Loveman and Simon [15] reported a similar example of erythema nodosum in which the lesion was reproduced by repeated administration of the sulfonamide drug. It was significant that in 3 of the 18 cases that showed a skin rash dermatitis of severe proportions developed.

Skin reactions were the most striking clinical evidence of sensitivity to the sulfonamide drugs. From this series of cases the conclusion appears to be justified that any skin reaction other than simple erythema should be a contraindication to the continued use of any member of this

group of drugs. The utmost care must be exercised and adequate clinical study maintained if a patient who has had any type of skin reaction is subjected to further use of sulfonamides. Repeated courses of sulfonamide treatment given to a patient once shown to be sensitive appeared to magnify the severity of the complications, as 14 patients who exhibited sensitivity had had two or more courses of the drug. A change in form of the drug appeared to reduce the hazard if sulfonamide therapy was reinstituted, but even then the reaction might be severe or fatal.

The prophylactic use of sulfonamide drugs against meningitis, gonorrhea, and other infectious diseases may well result in sensitizing patients to the drug, as noted by Lyons and Balberor,[16] Nelson,[17] Kalz and Steeves,[18] and Stiles.[19] While this possibility should not be considered a contraindication to the prophylactic use of sulfonamides, it must be recognized if fatal reactions are to be avoided. The protection afforded the majority is the paramount consideration, and should not be disregarded because death occasionally occurs in a sensitized individual. On the other hand, the dangers of the indiscriminate use of sulfonamide drugs for prophylaxis or in the therapy of minor infections cannot be overemphasized.

Conclusions

1. Striking histopathologic changes were seen in the material from 76 autopsies and in 2 additional specimens of skin taken for biopsy from patients who apparently had been sensitized to sulfonamides, as reviewed at the Army Institute of Pathology.

2. Characteristic acidophilic histiocytes were present in focal and diffuse infiltrations in the heart, liver, kidney, lung, spleen, lymph nodes, bone marrow, skin, testis, intestine, gallbladder, prostate, urinary bladder, skeletal muscle, thyroid, aorta, and meninges.

3. Significant vascular lesions were characterized by fibrinoid necrosis, endothelial edema, and proliferation.

4. Interstitial pneumonitis and hemorrhage by diapedesis in the pulmonary alveoli were attributed to sulfonamide sensitivity.

5. Focal subendocardial, subepicardial, and subpelvic renal hemorrhages were associated with typical acidophilic histiocytic infiltrates.

6. Sulfonamide crystals combined with calcium deposition were demonstrated in and adjacent to the distal convoluted and collecting renal tubules.

7. Evidence of individual susceptibility to initial and repeated courses of the sulfonamide group of drugs has accumulated in the literature and is substantiated by this series of cases.

8. Sensitization of large groups of patients with prophylactic doses of sulfonamide drugs may result in an increase in the number of histopathologic lesions encountered at autopsy. Many of these lesions were significant causes of death.

9. Increased caution must be observed in the prophylactic and therapeutic use of the sulfonamide drugs for minor infections.

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[*Illustrations follow*]

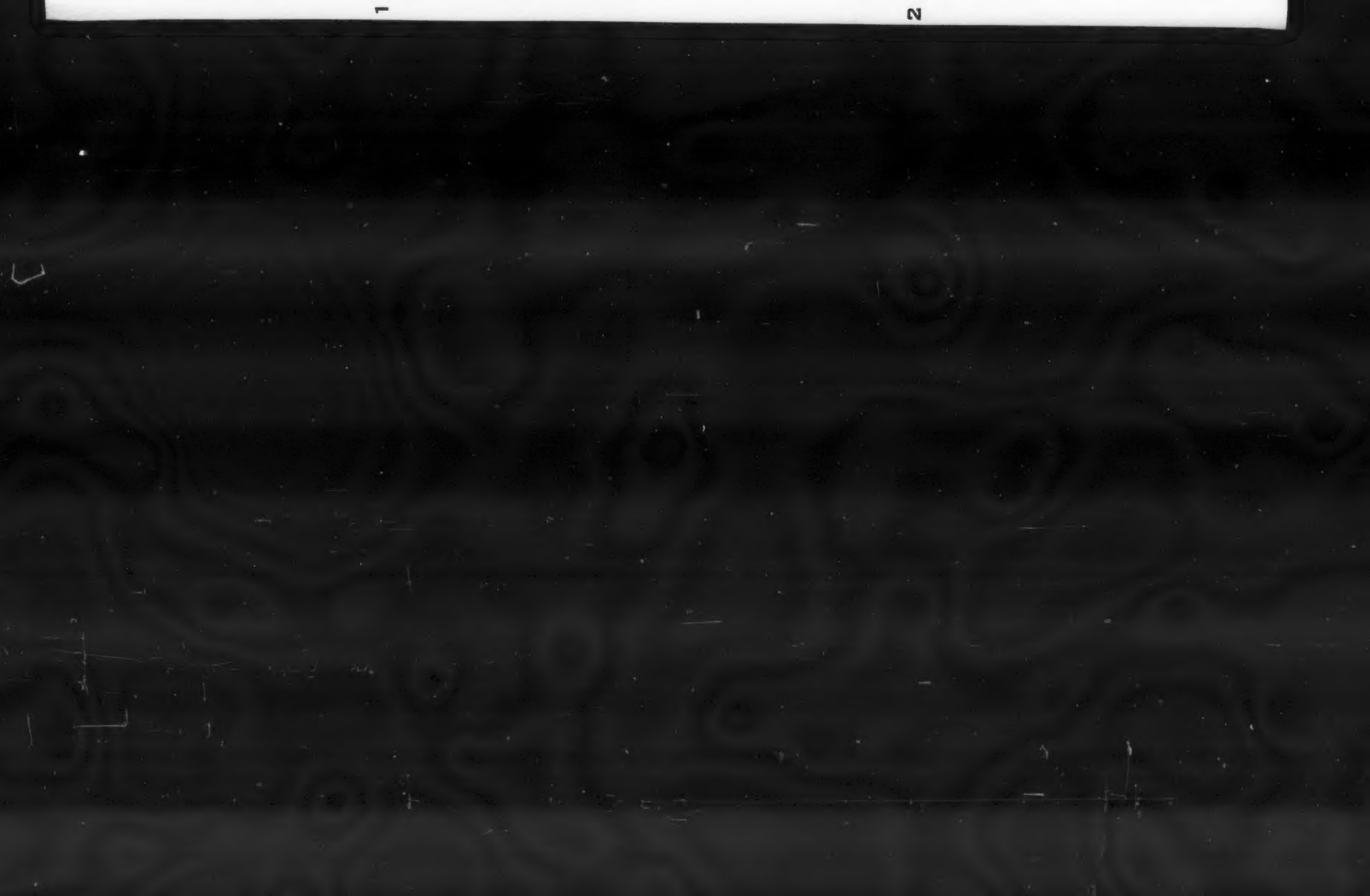
DESCRIPTION OF PLATES

PLATE 131

(A.I.P. = Army Institute of Pathology)

FIG. 1. Paravascular and interstitial infiltration of acidophilic histiocytes in the myocardium. Although monocytes predominate, a few polymorphonuclear cells are present also. × 240. A.I.P. neg. 79036.

FIG. 2. A small area in the upper right quarter of the preceding illustration is shown at a higher magnification. The many mononuclear histiocytes which occupy the greater part of the field were chiefly acidophilic. A few cells of the granulocyte series are included in the infiltration. The muscle fibers are not necrotic. × 1000. A.I.P. neg. 79039.



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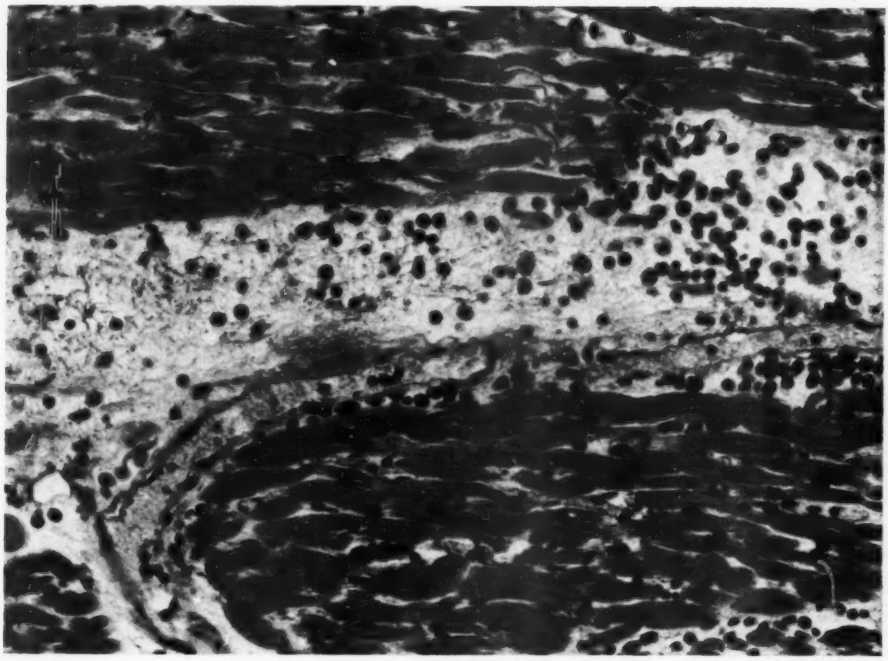

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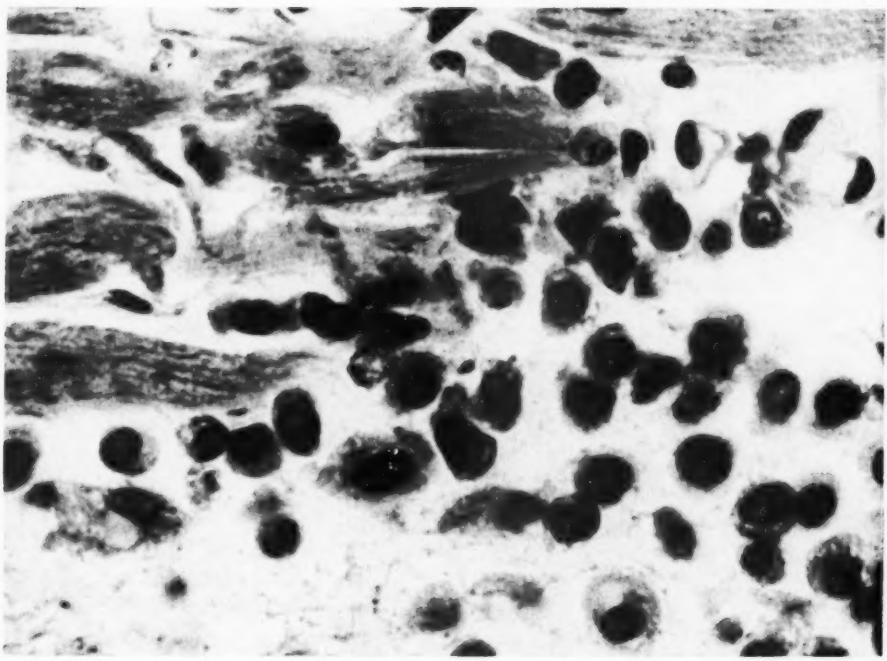
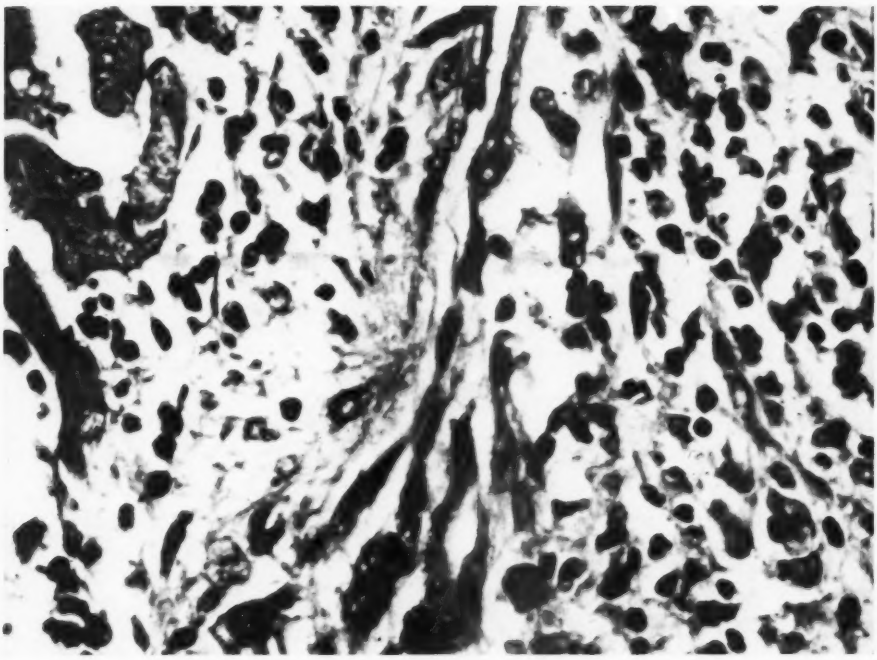
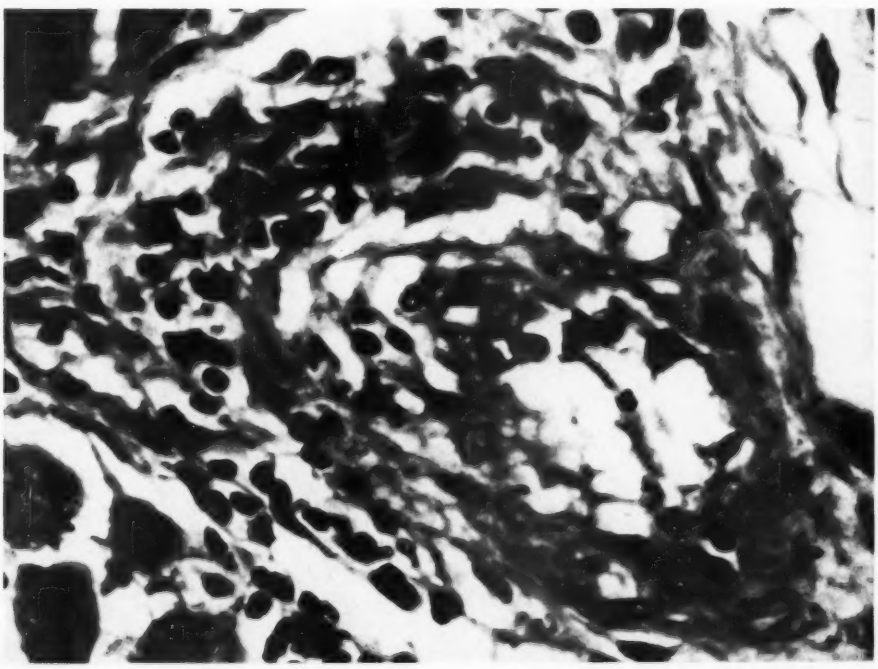


French Histopathologic Changes with Sulfonamides

PLATE 132

FIGS. 3 and 4. Fibrinoid necrosis is present in the walls of capillaries in the myocardium. The paravascular tissues are edematous and infiltrated with acidophilic histiocytes. There is active proliferation of capillary endothelium. × 700. A.I.P. negs. 79129 and 79132.





French Histopathologic Changes with Sulfonamides

PLATE 133

FIG. 5. Marked focal calcific deposits in myocardial fibers unassociated with primary vascular disease. The associated paravascular infiltrations of acidophilic histiocytes suggest a relationship to sulfonamide sensitivity. × 130. A.I.P. neg. 79040.

FIG. 6. Focal necrosis of hepatic parenchyma with acidophilic histiocytes composing part of the exudate. × 280. A.I.P. neg. 79041.

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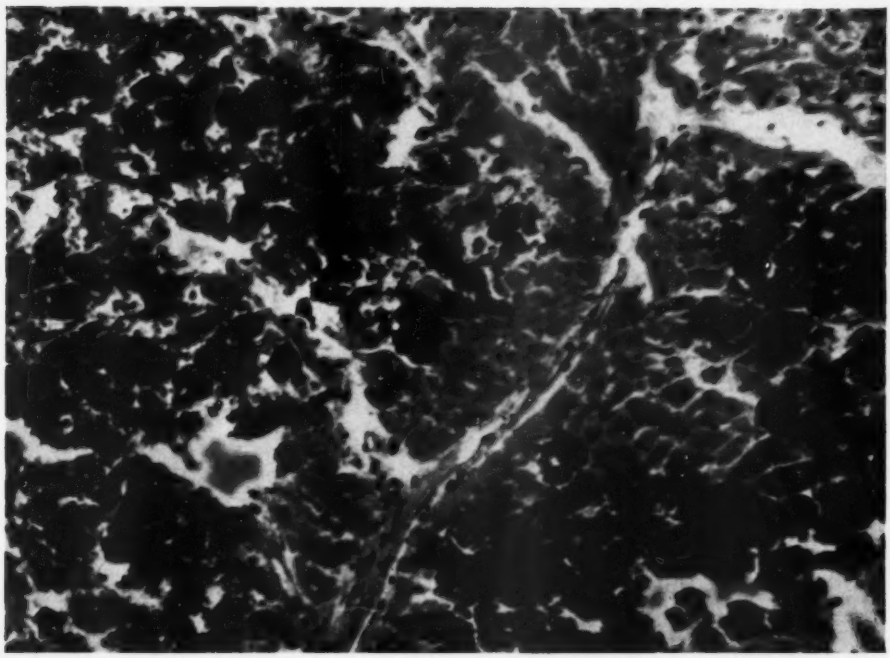

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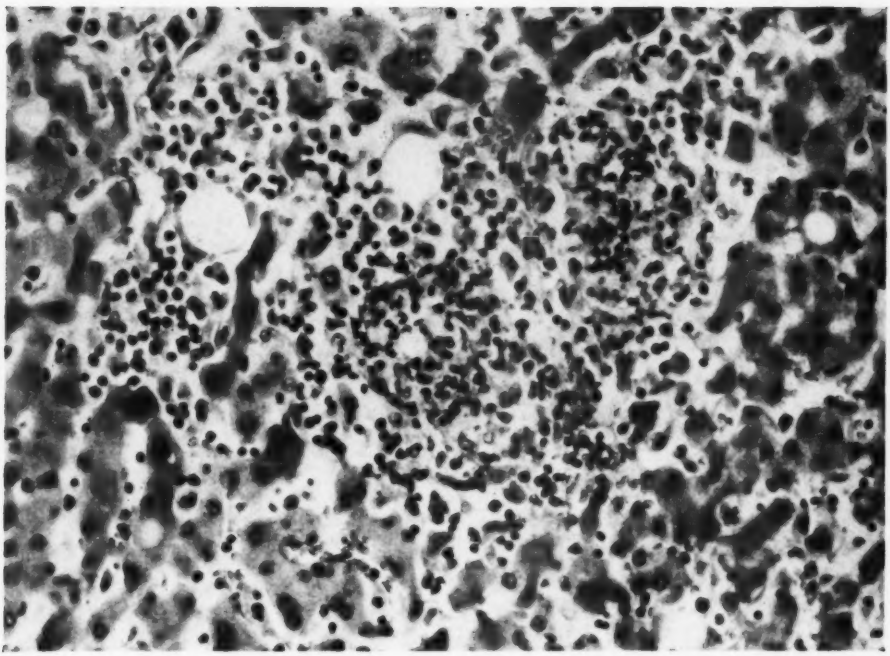

French Histopathologic Changes with Sulfonamides

PLATE 134

FIG. 7. Severe interstitial infiltration of acidophilic histiocytes and other inflammatory cells in the renal parenchyma. Acute parenchymatous degeneration of the epithelium of the tubules. × 200. A.I.P. neg. 79131.

FIG. 8. Crystals of acetylated sulfathiazole with slight calcific deposition in renal tubules. Interstitial infiltration of acidophilic histiocytes. × 915. A.I.P. neg. 79045.

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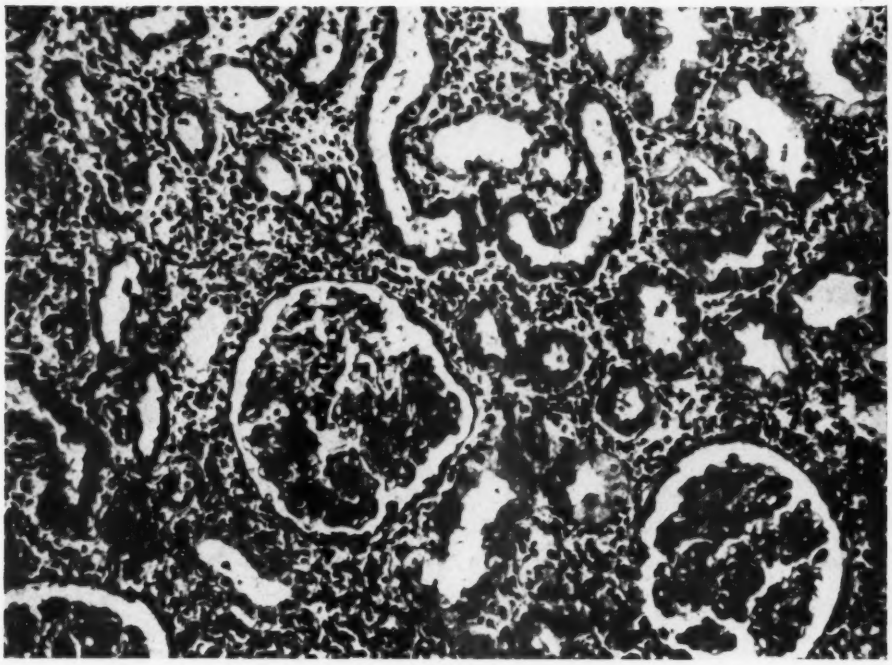

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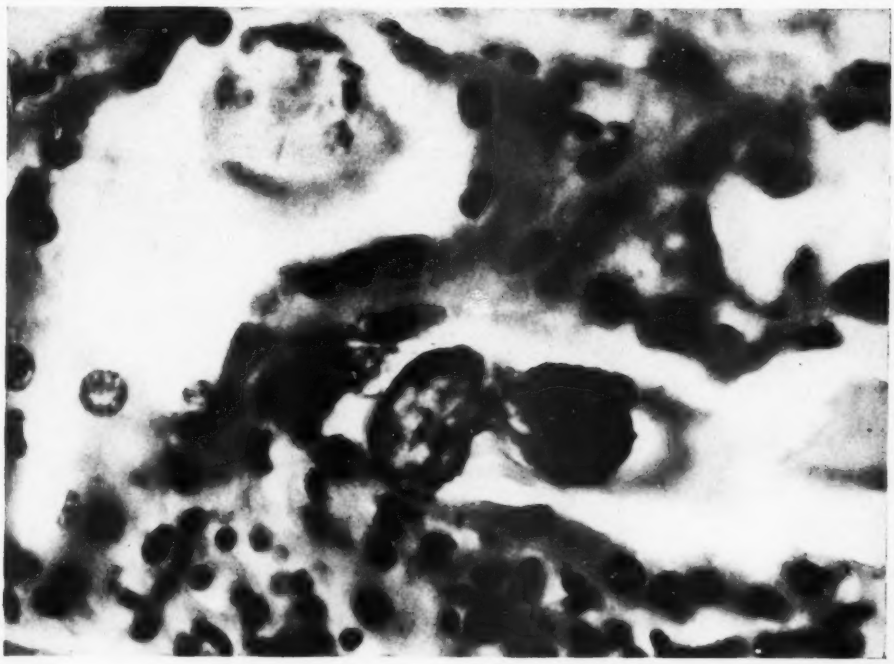

French Histopathologic Changes with Sulfonamides

PLATE 135

FIG. 9. Dermatitis with vesiculation in the superficial epidermis, resembling erythema multiforme and accompanied by a slight infiltration of acidophilic histiocytes in the dermis. × 96. A.I.P. neg. 79044.

FIG. 10. Granulomatous focus in the subcutaneous adipose tissue of the type of erythema nodosum. The paravascular character of the infiltration is evident here as elsewhere. × 120. A.I.P. neg. 79038.

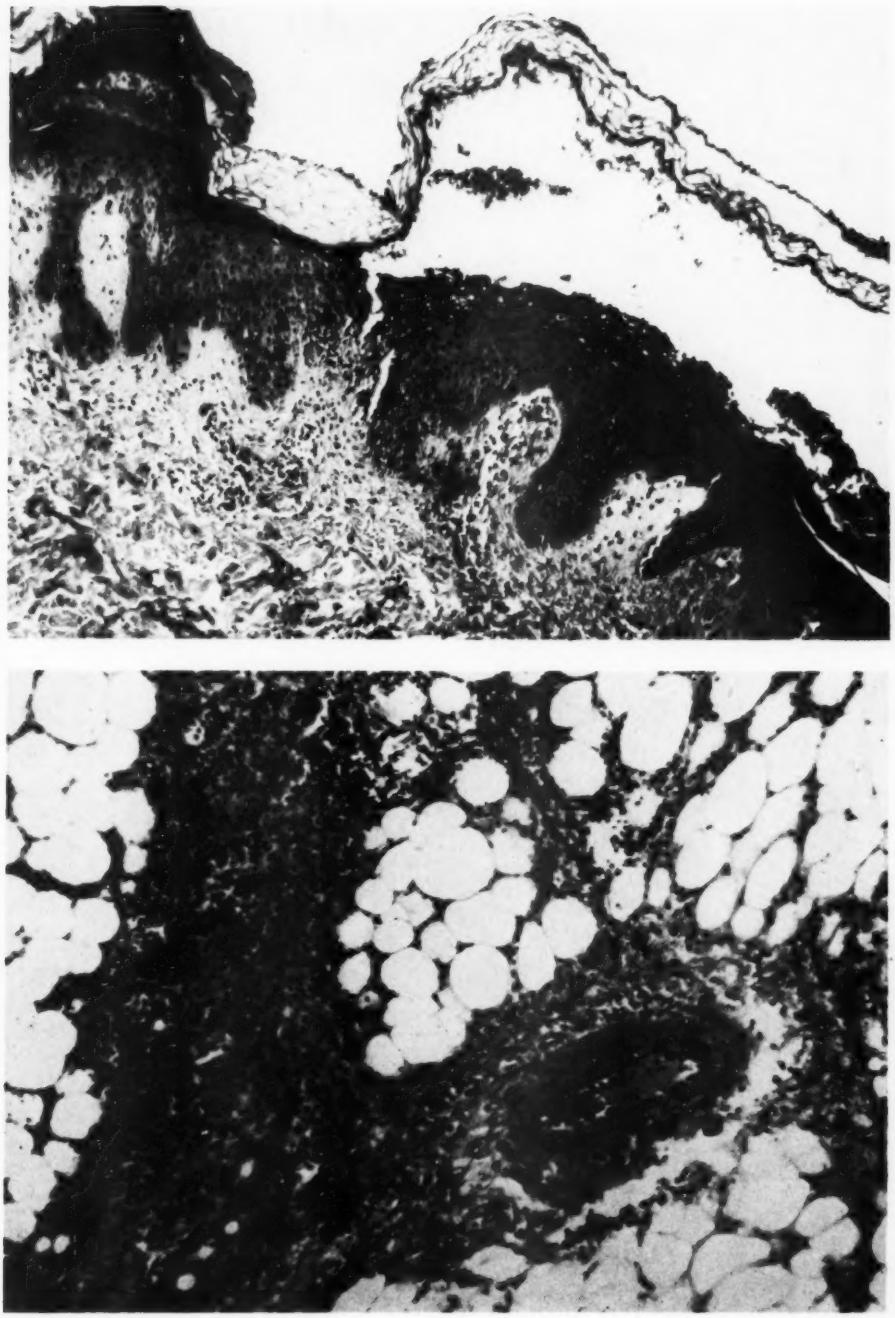

PLATE 136

FIG. 11. Acidophilic histiocytes infiltrate the interstitial tissues of the testis and are readily distinguishable from the larger interstitial cells of Leydig. The adjacent germinal epithelium shows active maturation. × 1000. A.I.P. neg. 79037.

FIG. 12. Small foci of necrosis are indicated in this area from the spleen by the chromatin dust which is present. Lymphocytes are decreased in the areas showing necrosis, and acidophilic histiocytes are abundant. × 350. A.I.P. neg. 79046.

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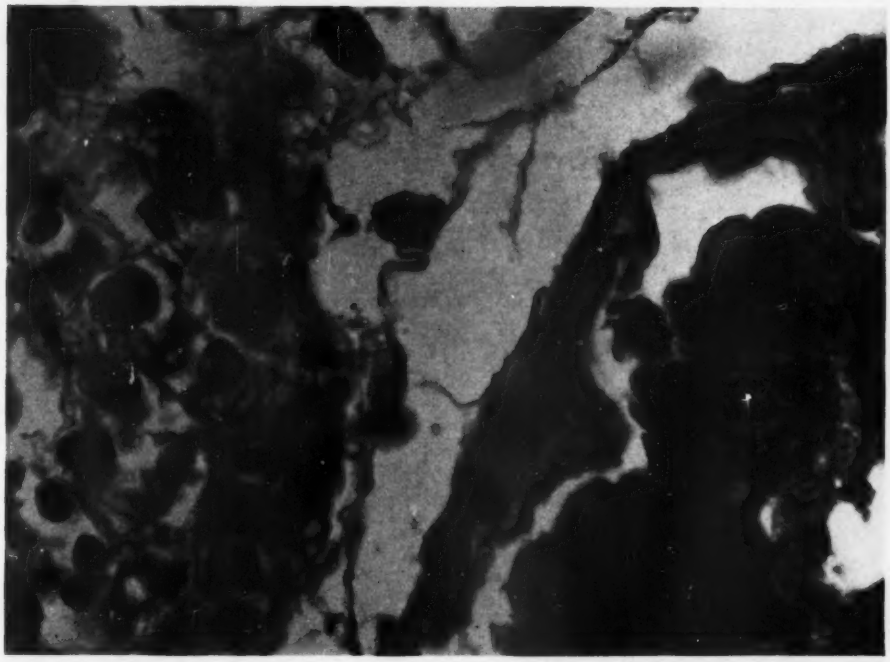

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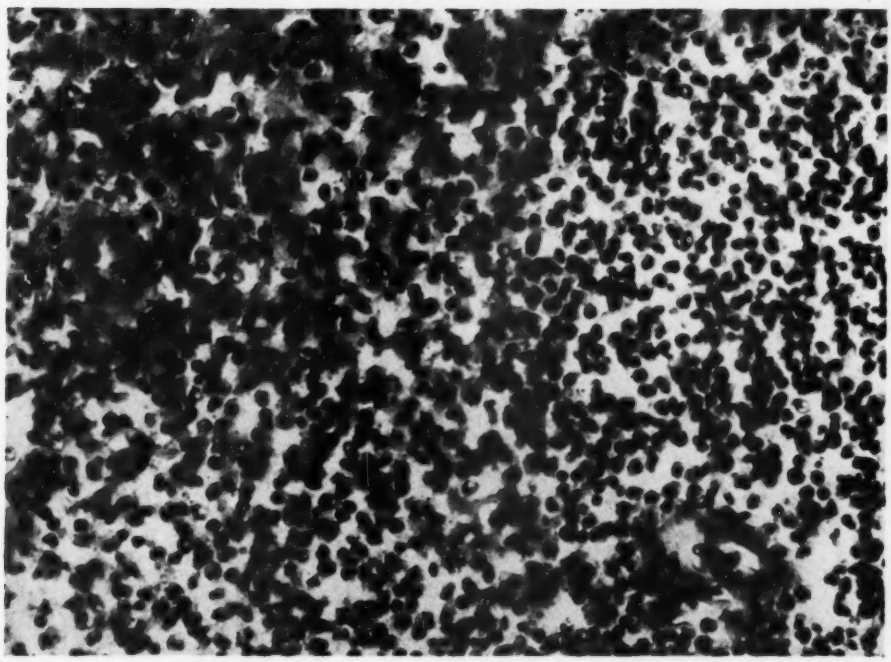

French Histopathologic Changes with Sulfonamides

PLATE 137

FIG. 13. Focal necrosis in a lymph node, with hyperplastic reticulo-endothelial cells. Acidophilic histiocytes are striking components of the cellular infiltration in the necrosed areas. × 350. A.I.P. neg. 79043.

FIG. 14. A paravascular focus in the wall of the gallbladder which is granulomatous and resembles the lesions of periarteritis nodosa. The predominant cell is the acidophilic histiocyte. × 330. A.I.P. neg. 79130.

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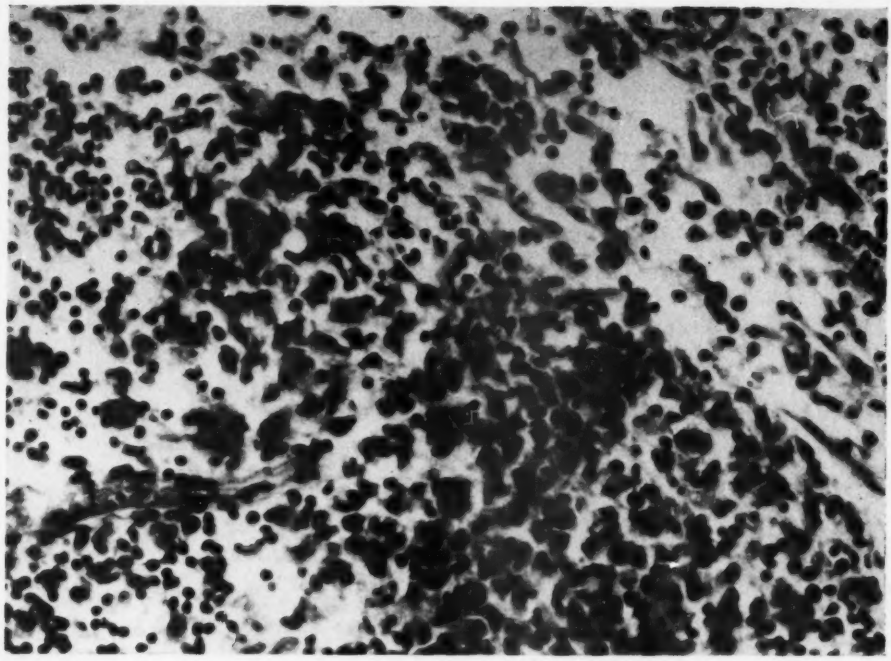

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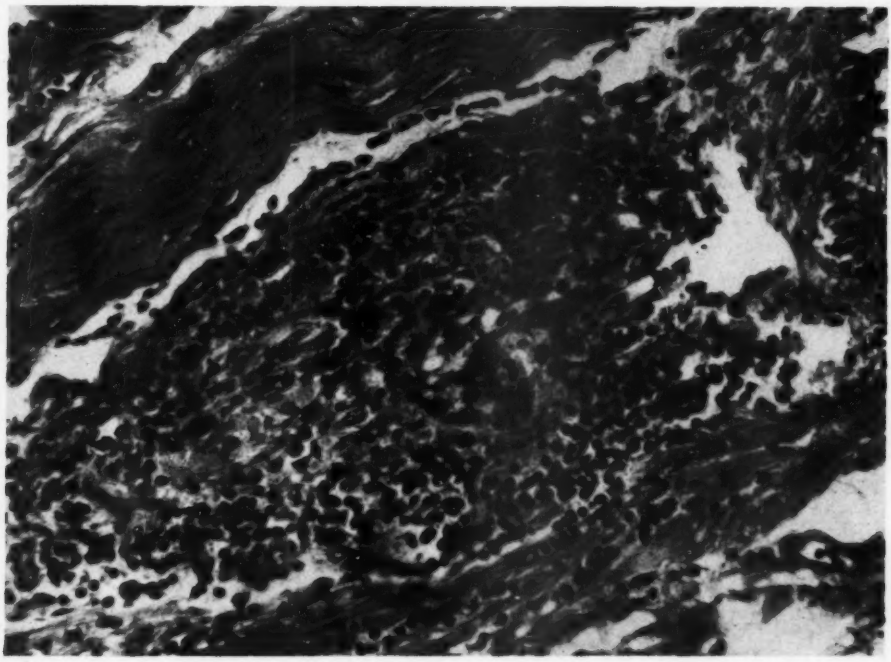

4

French Histopathologic Changes with Sulfonamides

THE PATHOLOGY OF SULFONAMIDE ALLERGY IN MAN*

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With the widespread use of the sulfonamide drugs, it soon became apparent that they sometimes caused untoward clinical results and even death.[1,2] A few of the patients who died had certain morphological changes that were attributed to sulfonamide therapy. Among the first of these lesions to be described were liver damage,[3] granulocytopenia,[4] and urolithiasis.[5] Further clinical and experimental studies rapidly enlarged the list of lesions caused by sulfonamide medication, and in 1942 French and Weller [6] showed that the heart and other organs could be affected. In 1943 Simon [7] presented a comprehensive review of the lesions attributable to the administration of the sulfonamide drugs. Since the publication of that review there have been many additions to the literature of sulfonamide lesions, but the emphasis, both clinically and pathologically, has remained upon the types of lesions reviewed by him. Those of the kidney, in particular, have continued to be reported frequently, while scant attention has been given to coexistent sulfonamide lesions.[8]

In the past few years 22 cases with sulfonamide lesions have been observed among the autopsies of this institute. The most common lesion encountered was a peculiar granulomatous reaction that has rarely been reported.[9-11] The series also contained several examples of a hitherto undescribed trabecular lesion of the spleen. Because this is the largest single group of cases of sulfonamide lesions yet studied, and because it contains many examples of both rare and common lesions, it provides a unique opportunity for the study of the morphology and pathogenesis of human sulfonamide lesions.

MATERIAL AND METHODS

To obtain the present series of cases, 2,000 autopsy protocols for the years 1940 to 1944 inclusive were reviewed. The autopsy records showed that 375 of these patients had received sulfonamide drugs. It is obvious that many more patients among the 2,000 probably had received sulfonamides, but it was considered scarcely feasible to trace these. An examination of the records and pathological material of the 375 sulfonamide-treated patients yielded 22 cases in which lesions attributable to sulfonamides were present. It is to be emphasized that only outspoken lesions without other demonstrable cause were accepted.

* Received for publication, December 4, 1945.

The 22 cases comprised 17 complete autopsies and 5 autopsies confined to the thorax and abdomen. Aerobic and anaerobic post-mortem blood cultures were done in 20 cases, while sections of sulfonamide lesions were stained to demonstrate acid-fast, Gram-positive, and Gram-negative organisms in all cases.

A control series of cases not treated with sulfonamide drugs was established by reviewing 400 autopsy cases from the pre-sulfonamide years of 1930 and 1931. These cases were consecutive and unselected save in two particulars only: partial autopsies and examinations of infants less than 1 month of age were excluded. Microscopical sections of the heart, liver, spleen, and kidneys were examined. Sections of bone marrow were not available. It can be stated at once that no lesions similar to those to be described in this paper were found in the control series except in association with an etiological agent that is known to produce such lesions, as, for example, the interstitial nephritis found in cases of scarlet fever, the myocarditis associated with diphtheria, and the granulomata of miliary tuberculosis.

General Analysis of Cases

An analysis of individual cases is presented in Table I. A more general consideration of the cases, as presented below, reveals that, preceding the administration of the sulfonamides, there were no factors common to these patients that appeared to determine the development of the lesions in question.

The patients were commonly of middle age, while the age extremes were 5 and 84 years. Eighty-two per cent were males in contrast to an autopsy population of 65 per cent males. The cases were drawn almost equally from the surgical and medical services, the clinical diagnoses being correspondingly diverse. At autopsy the state of nutrition was variable, 12 of the patients being well nourished, 6 being fairly well nourished, and 4 being in a state of poor nutrition.

While sulfathiazole was the sulfonamide compound most commonly employed, sulfanilamide, sulfapyridine, sulfadiazine, and sulfasuxidine were used in some cases. Daily dosages were always of the ordinary therapeutic amounts; total dosages varied from 75 to 3,100 grains.

Following the administration of these drugs several of the patients exhibited interesting and unexpected reactions which are detailed below. Four of the patients showed reactions that were obviously of an allergic nature. An additional 7 patients showed definite and frequently severe responses to the drugs, either during a long continuous course of therapy or, in some instances, immediately upon the institution of a further course of therapy. Two of the patients, cases 6 and 13, pre-

TABLE I

Analysis of Cases Showing Sulfonamide Lesions

	Clinical data					Sulfonamide lesions				
Case no.	Age and sex	Reason for sulfonamide therapy	Total dose (grains)	Cause of death (autopsy)	Remarks	Heart	Liver	Spleen	Kidneys	Other organs
1	33 M	Meningitis	1230 C* sulfapyridine	Granulocytopenia	Terminal febrile response with angina and cystitis; white blood cells, 1,600; red blood cells, 2,000,000; no granulocytes					Aplasia and focal necrosis of bone marrow
2	54 M	Supposed septicemia	195 C sulfapyridine	Myocardial failure and complications	No clinical reactions	Interstitial myocarditis; granulomata		•		
3	40 M	Gonorrhea	1500 C sulfapyridine	Granulocytopenia	Angina, jaundice, fever and delirium; white blood cell count rising after withdrawal of drug					Immaturity of bone marrow
4	31 M	Sinusitis	3 weeks' course of sulfanilamide	Acute glomerular and interstitial nephritis	Skin rash, conjunctivitis, swollen joints and fever; no drug for 7 weeks before death			Polyvasculitis; trabeculitis	Interstitial nephritis	
5	58 M	Postoperative fever	180 C sulfapyridine	Postoperative death (acoustic neuroma)	Hemorrhagic and exfoliative dermatitis		Granulomata	Trabeculitis		Dermatitis
6	84 M	Perineal inflammation	390 C sulfanilamide, sulfapyridine, sulfathiazole	Perineal infection, terminal pneumonia	Jaundiced for 5 days before death				Interstitial nephritis; polyvasculitis	Hyperplasia and immaturity of bone marrow

TABLE I—(*Continued*)
Analysis of Cases Showing Sulfonamide Lesions

	Clinical data					Sulfonamide lesions				
Case no.	Age and sex	Reason for sulfonamide therapy	Total dose (grains)	Cause of death (autopsy)	Remarks	Heart	Liver	Spleen	Kidneys	Other organs
7	37 M	Multiple traumata	585 C sulfathiazole	Traumata	No clinical reactions	Interstitial myocarditis; granulomata				Focal necrosis of bone marrow
8	66 M	Fever (simple fracture of leg)	1170 I† sulfathiazole	Polyvasculitis	Symptoms of vasculitis and vomiting with second course; terminal convulsions	Interstitial myocarditis	Granulomata; polyvasculitis	Trabeculitis	Interstitial nephritis; polyvasculitis; glomerulitis	Granuloma of fracture callus
9	48 M	Fever	338 C sulfathiazole	Exsanguination from acute peptic ulcer	No clinical reactions		Focal necrosis and hepatitis			
10	19 F	Pansinusitis and pneumonia	1365 I sulfathiazole, sulfadiazine	"Toxemia" and polyvasculitis	No clinical reactions			Trabeculitis	Interstitial nephritis; glomerulitis; granulomata	Polyvasculitis of sinuses and lungs
11	68 M	Fever	310 I sulfanilamide, sulfathiazole	Localized peritonitis, intestinal obstruction, sulfonamide lesions	No clinical reactions	Interstitial myocarditis; granulomata	Focal necrosis; granulomata		Granulomata	Focal necrosis of bone marrow; granulomata of peritoneum; polyvasculitis of prostate
12	50 M	Empyema thoracis	1170 C sulfathiazole	Perforated peptic ulcer, sulfonamide lesions	No clinical reactions	Granulomata		Trabeculitis	Interstitial nephritis; granulomata	
13	56 M	Prophylactic (carcinoma of urinary bladder)	75 I sulfathiazole	Massive pulmonary embolism	Questionable febrile reactions		Granulomata		Granulomata	

	Clinical data					Sulfonamide lesions				
Case no.	Age and sex	Reason for sulfonamide therapy	Total dose (grains)	Cause of death (autopsy)	Remarks	Heart	Liver	Spleen	Kidneys	Other organs
14	68 M	Septic course	345 I sulfathiazole	Renal failure, myocarditis	No clinical reactions	Interstitial myocarditis	Granulomata		Granulomata	
15	42 F	Pneumonia	418 I sulfathiazole	Heart failure, polyvasculitis	Temperature rose 3.8 F. 24 hours after first dose of second course		Polyvasculitis; granulomata	Trabeculitis	Granulomata	Granulomata of lung and bronchus
16	5 M	Upper respiratory infection	165 C sulfadiazine	Postoperative (C.N.S.) death	No clinical reactions		Granulomata			
17	31 M	Meningitis	450 C sulfadiazine	Tuberculous meningitis	No clinical reactions					Polyvasculitis of renal pelvis
18	47 F	Prophylactic	370 C sulfathiazole	Massive pulmonary embolism	Asthmatic attacks; history of asthma				Interstitial nephritis; granulomata	
19	63 F	Empyema thoracis	1260 I sulfathiazole, sulfadiazine	Massive hepatic necrosis	Jaundiced 2½ days after first dose of final course; immediate fall of fever; died in 6 days		Massive necrosis			
20	58 M	Prophylactic	232 I sulfathiazole	Massive hepatic necrosis	Jaundiced 28 hours after first dose of second course; history of bronchitis; died in 3 days		Massive necrosis			
21	51 M	Ulcerative colitis	3100 I sulfasuxidine	Colitis and sulfonamide lesions	Conjunctivitis; sulfonamides 1 year previously	Interstitial myocarditis; granulomata	Granulomata		Interstitial nephritis; granulomata	Focal necrosis of bone marrow
22	49 M	Postoperative pneumonia	150 C sulfathiazole	Sulfonamide reaction with anuria	Chill, fever, oliguria, delirium, convulsions; sulfonamides 2 years previously				Nephrosis	

* C—Continuous course of therapy.
† I—Interrupted course of therapy.

sented reactions of a suggestive but questionable character. The remaining 9 patients suffered no unfavorable clinical reaction to the sulfonamides.

The 4 patients who exhibited clinical allergic reactions were as follows:

Case 4. This patient was given a 3 weeks' course of sulfanilamide for sinusitis. At the termination of the course there developed painful and swollen joints, a skin rash, conjunctivitis, and fever. He lived for 7 weeks, receiving no further sulfonamide.

Case 5. This patient was given 180 grains of sulfapyridine because of a fever that occurred after the removal of an acoustic neuroma. A severe hemorrhagic and exfoliative dermatitis developed which dermatological consultants attributed to the sulfonamide.

Case 18. This patient had acute cholecystitis and was given 370 grains of sulfathiazole in a continuous course. There was a history of asthma, and the drug appeared to induce asthmatic attacks.

Case 21. This patient suffered from chronic ulcerative colitis. On two occasions during the previous year he had been given sulfonamides without untoward reactions. On his final admission he received 3,100 grains of sulfasuxidine in an interrupted course. Four days before death conjunctivitis developed.

The remaining 7 patients who suffered untoward clinical reactions to sulfonamide therapy are as follows:

Case 1. This patient presented signs and symptoms leading to a diagnosis of meningitis. He was given 1,230 grains of sulfapyridine in a continuous course. Terminally, angina and cystitis developed, while his white blood cell count fell from a high level to 1,600 and no polymorphonuclear leukocytes could be found in the blood. The red blood cell count fell to 2,000,000. The temperature rose from 98° to 107°F. during the terminal 6 days (Text-Fig. 1-a).

Case 3. This patient was given 1,500 grains of sulfapyridine in a continuous course of treatment for gonorrhea. When admitted to the hospital there were granulocytopenia, jaundice, angina, fever, and delirium.

Case 8. This patient was hospitalized for a simple fracture of the tibia and fibula. He was given 1,170 grains of sulfathiazole in an interrupted course for an upper respiratory infection. His initial exposures to the drug were without untoward reactions, but the final course caused nausea and vomiting, while the signs and symptoms of periarteritis nodosa developed at the same time.

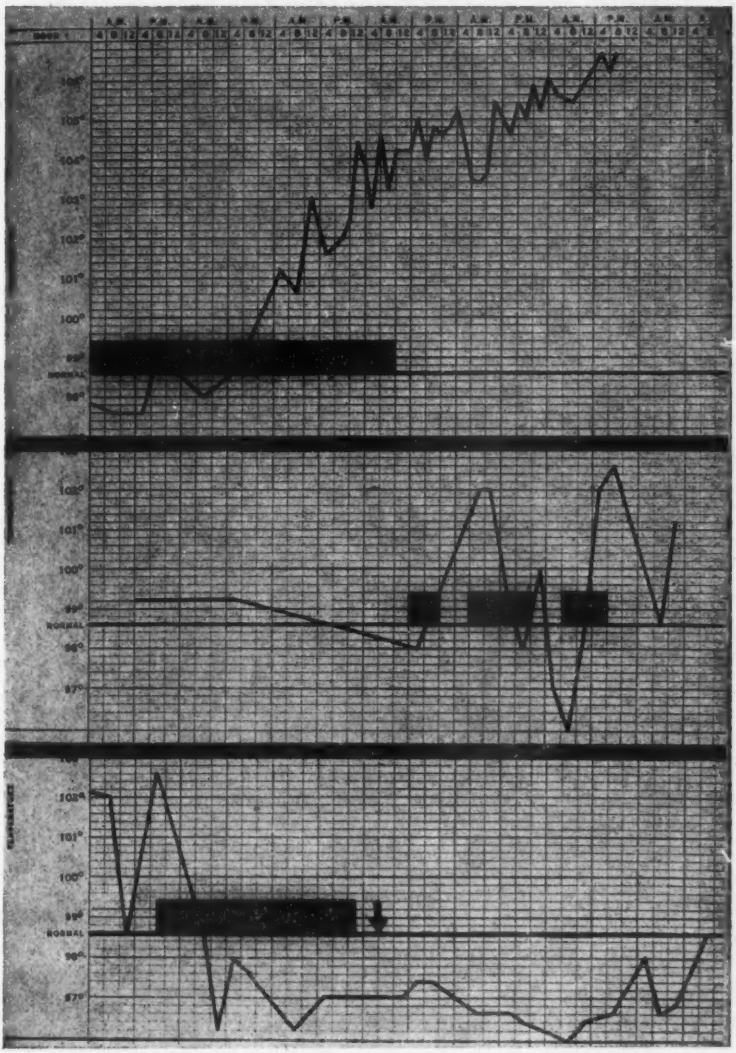
Case 15. This patient had coronary heart disease and was given 418 grains of sulfathiazole in an interrupted course for suspected pneumonia. The initial exposure to the drug caused no untoward reaction, but the final course, administered after an interval of 3½ weeks, caused the temperature to rise 3.8°F. within 24 hours (Text-Fig. 1-b).

Case 19. This patient had an empyema thoracis and was given 1,260 grains of sulfathiazole and sulfadiazine in an interrupted course over a period of 2 months. The first courses of therapy were without unusual reactions, but jaundice occurred 2½ days after the first dose of the final course was given, and the patient died 3½ days later from acute hepatic insufficiency (Text-Fig. 1-c).

Case 20. This patient had a very similar reaction to that in case 19. He was given 232 grains of sulfathiazole in an interrupted course. Again, there were no untoward reactions with the first exposure, but jaundice appeared 28 hours after the first dose of the second course and the patient died of acute hepatic insufficiency within 3 days. This patient had a history of seasonal bronchitis.

Case 22. This patient was known to have received sulfonamides 2 years pre-

viously with satisfactory effect. On his final admission he was operated upon for the repair of a ventral hernia. On the day following operation he produced 470 cc. of urine and was given sodium sulfathiazole in glucose-saline solution intravenously. One-half hour after this treatment the patient suffered a chill; delirium, convulsions, and severe oliguria followed. On the 3 succeeding days he produced 195, 22,



Text-Fig. 1 (a, b, and c). Terminal temperature readings of cases 1, 15, and 19. The heavy black blocks indicate the period of sulfonamide therapy. The arrow in Figure 1-c indicates the development of visible jaundice.

and 50 cc. of urine. Death occurred 4 days after the sulfonamide was first given. A total of 150 grains of the drug was used. Clinically, death was attributed to a severe sulfonamide reaction.

Among the 22 cases in which sulfonamide lesions were found, it is our opinion that these lesions caused the death of 7 patients, were a major factor in the death of 7 patients, and were of minor or negligible importance in the death of 8 patients.

Pathology of Sulfonamide Lesions

The lesions encountered in the 22 cases, and which we ascribe to sulfonamide therapy, fall in the main into the morphological classification of necrotic, granulomatous, interstitial inflammatory, and polyvascular inflammatory groups, and a small miscellaneous group. In many cases the lesions were not purely of one type, and combined or intermediate forms existed. In most cases the lesions were microscopic. In only 3 instances were they visible to the naked eye. The gross appearance of the sulfonamide lesions in these 3 cases will be described under their appropriate headings below.

Necrotic Lesions

Necrosis of the liver was the predominant lesion in 3 cases, while focal necrosis of the bone marrow was observed in 3 other instances. In all types of sulfonamide lesions studied, severe degeneration and necrosis were always minor and variable concomitants.

Liver. Two cases of massive hepatic necrosis presented in the gross a shrunken, soft liver with a wrinkled capsule of mottled yellow and purple color. On section one liver presented a fairly uniform, smudgy, yellow surface with loss of the normal markings. The cut surface of the liver in the other case showed patchy yellow areas with a loss of normal markings. These areas were irregular in outline, measured up to 4 cm. in diameter, and were often confluent. Microscopically, this extensive necrosis took the form of widespread, confluent central necrosis associated with hemorrhage into the areas of necrosis, and marked hyperemia of the sinusoids throughout the rest of the liver. The spaces of Disse were ballooned with amorphous eosinophilic material. In the areas of recent necrosis an almost normal outline of liver cells was retained, but their cytoplasm was waxy and eosinophilic and the nuclei had either disappeared or showed karyolysis. The most striking feature of these necrotic areas was the good preservation of the Kupffer cells and the increased number of nucleated cells in the sinusoids of the necrotic areas and of the adjacent better-preserved areas. Some of the cells were polymorphonuclear leukocytes, but for the most part they were large mononuclear cells, representing either an accumu-

lation of blood-borne monocytes, or a proliferation of reticulo-endothelial cells *in situ*. In the greater portion of both livers the necrosis was so extensive and advanced that the liver simulated closely the gross and microscopical appearance of acute yellow atrophy. However, there was no evidence of regeneration of liver cells or bile ducts. Only a few liver cells about the portal areas and a few of the perilobular bile ducts maintained a normal appearance. Reticulin stains revealed a remarkably good preservation of the architecture of the reticulin framework, and this probably accounted for the relatively good preservation of the liver cord architecture. The liver in the third case, while showing necrosis, might be classified equally well as an example of interstitial hepatitis. The lesion in this instance showed a very severe focal degeneration of liver cells. Individual liver cells displayed eosinophilic necrosis or dissolution associated with marked disorganization of the liver cords. The most striking feature of this lesion was the large number of well preserved mononuclear cells in the sinusoids between the necrotic liver cords. The sinusoids were filled with eosinophilic débris containing a few polymorphonuclear leukocytes and eosinophils. There was a very close similarity between this lesion and those seen in the less damaged areas of the livers of the 2 cases described above, and it appeared to be merely a phase in the development of the more massive necrosis (Fig. 1).

Bone Marrow. Focal necrosis of bone marrow was associated in one case with aplasia and in 2 with a very cellular marrow, exhibiting immaturity of the myeloid elements. These areas of necrosis appeared as irregular but well circumscribed pale patches. This pallor was due to a loss of cells and of the normal reticular structure which was replaced by an amorphous mass of eosinophilic tissue débris. There were no pyknotic nuclei in the necrotic areas of the hypoplastic marrow. However, in these necrotic areas there were even fewer cells than in the rest of the marrow. In the two cellular bone marrows showing immaturity, the pale patches of focal necrosis were pronounced, and in these the washed out background was peppered with many irregularly fragmented and pyknotic nuclei. The areas of focal necrosis in all cases failed to show the normal reticular framework with special stains. Moreover, in the hypoplastic marrow, the widespread fuzzy, granular, disrupted appearance of the supporting framework was associated with a loss of the reticulin network as demonstrated by special silver stains.

Granulomatous Lesions

Lesions of granulomatous character were those most commonly encountered in our series, occurred in a well advanced stage in 13 of the 22 cases, and involved a total of 25 organs. They were found in the

heart in 5 cases, in the liver in 8, in the kidneys in 8, and in the lung and bronchus, the callus of a fracture, and in the peritoneum, each in one case. In only one case (no. 21) were these lesions visible grossly. In this case they could be seen in the heart, liver, and kidneys, and in these organs they formed well demarcated gray spots varying in size from a barely visible speck up to 3 mm. in diameter. The granulomata were, in many cases, associated with minimal to advanced degeneration of the parenchyma of the organ involved. In some cases an interstitial inflammation accompanied the granulomatous reaction. There was no difficulty in separating the two entities on morphological grounds although a pathogenetic distinction was not so apparent.

The granulomata, in whatever situation they occurred, were definitely of focal character with an irregular but well defined outline. The architecture of the adjacent parenchyma was usually well preserved, even though some degree of cytoplasmic degeneration existed in the nearby cells (Figs. 2 to 4). Characteristically, the granulomata presented a uniform cellular pattern from the center to the periphery of the lesion, producing a tessellated appearance. This mosaic appearance was due to the uniform and closely packed arrangement of large mononuclear cells with somewhat irregular, blunt, basophilic nuclei set closely and uniformly. The cytoplasm of these cells was abundant but pale (Fig. 4). The dominant cell of the lesion was always of a large mononuclear type. In addition, there were lesser and varying numbers of plasma cells, lymphocytes, polymorphonuclear leukocytes, and eosinophils.

The eosinophilic background of the lesion consisted of the necrotic parenchyma of the organ involved. This necrosis was usually so complete that it showed a total loss of the original cells and architecture, and there remained only a granular, eosinophilic mass of débris. In this background pyknotic and fragmented nuclei were seen, presumably derived also from the necrosis of the original cells of the parenchyma. Eosinophils, when present, were easily identified and were sometimes very numerous. However, since they were often absent, they were not considered a necessary characteristic of the lesion. In the earliest stage of development of the granulomata, partially preserved remnants of the original parenchyma were still present (Fig. 2). Sometimes within one organ well developed granulomata were associated with other focal areas of varying degrees of degeneration and cellular infiltration, which we regarded as representing various stages in the development of the granuloma. Some of these focal areas presented only focal degeneration, while others showed many necrotic cells with a slight mononuclear cellular infiltration, and, finally, there were some

areas consisting predominantly of large mononuclear cells among which an occasional necrotic cell of the original tissue could be seen (Fig. 3).

Heart. In the heart the granulomatous lesions were found occasionally in the intermuscular septa extending between adjacent muscle fibers. More often they replaced areas of muscle in the myocardium. In the center of these latter lesions the myocardial fibers were completely lost although reticulin stains revealed that the sarcolemmal sheaths were preserved in the midst of the cellular reaction. At the margin of these focal lesions the muscle fibers were usually necrotic, presenting the appearance of Zenker's necrosis (Figs. 5 and 6). These necrotic fibers were separated by a light infiltration of varying inflammatory cells (Fig. 5), producing a somewhat similar appearance to the interstitial inflammation of the heart to be described later.

Liver. In the liver the granulomata were most often found in the portal areas, but they also occurred with less frequency in all other parts of the lobule. In the involved portal areas bile ducts were the only original structure remaining recognizable. Sometimes there was a suggestion of a small arteriole from which the cellular reaction radiated, so that the granuloma appeared to center on an "exploded" portal arteriole (Fig. 10). Occasionally an appearance of fibrinoid degeneration of the collagen was present. When the granulomatous lesions were found in the parenchyma, there were usually an associated complete loss of liver cells (Fig. 4), and partial destruction of the reticulum. In a few instances there were focal areas of recent necrosis of still recognizable liver cells associated with an accumulation of cells like those of the fully developed granuloma (Fig. 3). In one case the liver showed well developed granulomata and also contained recent foci of necrosis. Pyknotic liver cell nuclei could be seen in these areas, and the Kupffer cells were well preserved, but there was only a minimal mononuclear cellular reaction in the necrotic areas (Fig. 2).

Kidney. In the kidney the granulomata were often associated with a more widespread interstitial infiltration than was usual in other organs. In many cases a generalized severe degeneration of the convoluted tubules was present. The granulomata were found more often in the cortex than in the medulla. The lesions were not so well circumscribed in the kidney as in the heart and liver, and cellular infiltration extended in an irregular manner between the glomeruli and tubules in the region of the granuloma. The most characteristic feature of the lesion as found in the kidney was the presence of recognizable fragments of renal tubules in the midst of well developed granulomatous lesions (Fig. 7). Plasma cells and especially eosinophils were generally more numerous in the kidney than in similar lesions in other organs. In one case well

developed renal granulomata were definitely peritubular in position so that the tubules were compressed and distorted, forming a nucleus of severely injured tubular cells at the center of each lesion (Fig. 9). Eosinophils were very numerous among the infiltrating cells in this case. In a few instances multinucleated giant cells of irregular shapes and of undetermined origin were found in granulomata of the kidney.

Lung and Bronchus. A single example of granuloma of the lung showed a necrotic granulomatous lesion in a patch of organizing pneumonia. A perivascular granuloma was present in the bronchus of the same case.

Peritoneum. One example of granuloma of the peritoneum due to the local application of sulfathiazole was encountered. Its most striking feature was the presence of numerous multinuclear giant cells of foreign body type.

Bone Callus. A single example of granuloma was found in the fibrous tissue of the callus of a simple fracture of the tibia.

Interstitial Inflammatory Lesions

Interstitial inflammatory lesions were found in the heart in 6 cases, in the kidneys in 7 cases, and in the liver in 1 case, totalling 11 patients in all. As already pointed out, this interstitial inflammatory lesion sometimes blended with the borders of definite granulomata in the heart and kidneys.

Heart. The characteristic feature of the myocarditis in these cases was an infiltration of large mononuclear cells occurring in the fine intermuscular septa. Small and varying numbers of neutrophils and eosinophils were usually scattered among the large mononuclear cells, although in some cases eosinophils were absent. Occasionally the muscle fibers bordering these areas showed Zenker's necrosis. Only rarely did a large intermuscular septum show cellular infiltration. In those hearts with granulomatous lesions there was some adjacent interstitial infiltration of mononuclear cells, and this was associated with recent necrosis of muscle fibers (Fig. 5).

Liver. The interstitial inflammatory lesion of the liver has already been described as an example of hepatic necrosis. The marked interstitial inflammatory response present in this case also warrants its inclusion under this heading (Fig. 1).

Kidney. In the kidney the interstitial infiltration was of small extent in some cases, while in others it was very extensive. It was found in the cortex and medulla, or both. There was usually a severe nephrosis of cortical and medullary tubules. In one case (no. 4) there was a severe interstitial nephritis associated with a peculiar glomerulitis

unlike any recognized renal glomerular lesion. In contrast to the myocarditis, the predominant cells of the renal lesion were plasma cells and eosinophils. Occasionally the lesion appeared necrotic, with pyknotic nuclei in both the tubules and the cellular infiltration. In distinction to the combined interstitial and granulomatous lesions of the heart, granulomata and interstitial inflammation of the kidney were not sharply demarcated from one another.

Polyvascular Inflammatory Lesions

Polyvascular lesions were found in 7 cases. The vessels involved included those of the spleen, liver, kidney, lung, air sinus, prostate, and renal pelvis. The vessels varied from the size of the afferent glomerular arterioles of the kidney to arteries of 300 μ in diameter. Typically, there was a compact, granular eosinophilic smudginess of all layers of the vessel wall with complete loss of muscle nuclei. Frequently there existed a considerable degree of separation of the necrotic elements, so that the intima bulged into the lumen. The affected vessel was surrounded by a varying depth of large mononuclear cells, a few polymorphonuclear leukocytes, and rare eosinophils. Only rarely was there a definite infiltration of inflammatory cells in the muscle layers (Figs. 11 and 12).

Liver. In the liver the polyvascular lesion presented itself in two forms. In one the vessel appeared to be the center of reaction. The vessel wall was necrotic and there was some adventitial and periadventitial cellular infiltration for only a short distance beyond the vessel wall. This was the less common form. The other more common expression of polyvasculitis in the liver usually involved a whole portal area in the form of a granuloma which merged with the adventitia of the necrotic portal vessels. Sometimes only remnants of an exploded vessel could be made out in the center of a granulomatous reaction (Fig. 10).

Kidney. Polyvasculitis of the kidney affected arteries and arterioles. The arteriolar reaction consisted of an irregular line of inflammatory cells following the course of the necrotic afferent arteriole as though being led up to the hilum of the glomerulus. Small fragments of eosinophilic material could be made out lying in this cellular infiltration, probably representing portions of necrotic vessel walls. Some of the corresponding glomeruli presented a varying degree of cellular infiltration involving varying portions of the glomerular tuft. The destruction and cellular infiltration of the glomerulus appeared to extend centrifugally from its hilus. In some cases only the hilar half of a glomerulus was affected, presenting an appearance as though the entering arteriole and proximal part of the glomerulus had been the center of a violent

explosion, while leaving the distal portion of the glomerulus untouched. In others, there was almost total disintegration of the entire tuft which was infiltrated by cells with elongated nuclei arranged in a radial pattern. The cells were again predominantly large mononuclear cells.

In both liver and kidney the lesions presented much of the appearance of the granulomata, but in the polyvascular lesion a necrotic vessel was at the center and there was more necrosis, a more acute cellular response, and less compactly arranged cells. In the spleen this polyvasculitis was sometimes part of the trabeculitis to be described.

Trabeculitis of the Spleen

A peculiar necrotic and inflammatory lesion was found in the trabeculae of the spleens of 6 cases. The term trabeculitis has been coined to describe this singular inflammatory lesion. Only a few of the trabeculae in any single section were involved. They showed edema of their collagen, irregular areas of fibrinoid necrosis, and, in sections stained to demonstrate elastic tissue, an almost complete loss of the normally prominent elastica. The normal, compact, fibrillary structure of the collagen bundles was separated, producing a ragged, swollen and frayed trabecula that appeared to melt away in the pulp. Scattered through and around the involved trabeculae were large mononuclear cells. With these cells there was a variable admixture of polymorphonuclear leukocytes. In the most necrotic parts of a trabecula and along its margin abscess-like collections of polymorphonuclear leukocytes were sometimes found (Fig. 8). In one case there could be seen in the center of the most severely damaged areas necrotic arterial walls that appeared to have exploded. In this case the vascular remnants were surrounded by showers of pyknotic nuclei (Fig. 11). However, in all other cases, the changes in the trabeculae were unassociated with vessel destruction, and the lesion was present as an inflammation of the fibrous structure of the trabecula alone.

Nephrotic Lesion

A pure nephrosis without inflammatory cellular infiltration was encountered in only one case (no. 22). In this case the convoluted tubules showed a marked degree of degeneration with vacuolation of cytoplasm. The nuclei of the majority of the epithelial cells of the tubules were slightly pale and swollen. A rare nucleus showed pyknosis. Bowman's spaces and the convoluted tubules were dilated and filled with flocculent eosinophilic material. The collecting tubules of cortex and medulla showed a similar dilatation, their lumina containing fuzzy precipitate or frequent hyaline casts.

Degenerative Changes

Many of the cases showed a degree of parenchymatous degeneration that is not usually seen in routine autopsy material. For example, in the kidney the glomeruli often appeared larger than normal and their basement membranes swollen, while in the liver there were cloudy swelling, fatty changes, and disorganization of the liver cords. Such changes, of course, are completely nonspecific.

Discussion

Etiology

In spite of the inherent difficulty of proving the cause of lesions in a morphological study of this kind, we believe that the lesions described above were produced by sulfonamide medication. This conclusion seems warranted because no other cause was found which could satisfactorily explain their development, and because sulfonamide therapy was the only factor common to all of the cases in which more or less identical lesions were encountered, as already described. Many of these lesions are identical with lesions previously described by others and attributed to sulfonamides, and many have been reproduced in experimental animals by sulfonamides.

For example, focal necrosis of the bone marrow,[12, 13] aplasia and immaturity of the bone marrow,[14] agranulocytosis,[4] and massive hepatic necrosis [3] have been recognized as sulfonamide lesions for several years. Focal necrosis of the liver with hepatitis,[15] interstitial myocarditis,[6] interstitial nephritis,[16] and the granulomatous foreign body reaction caused by the local application of sulfathiazole to the peritoneum [17] are also well established lesions. A lesion that has been less frequently reported is sulfonamide nephrosis with anuria occurring in the absence of urolithiasis medicamentosa. Prien [18] has discussed the pathological differences that exist between this type of nephrotic anuria and that due to the deposition of sulfonamide crystals. Recently, Rich [19, 20] has described cases showing lesions indistinguishable from periarteritis nodosa which he has attributed to sulfonamide medication. Among our 22 cases we found 7 with polyvascular lesions due to sulfonamides which differ in several details from those studied by Rich. We believe that the variations which we find among our own cases of sulfonamide polyvasculitis and between them and Rich's cases of sulfonamide periarteritis nodosa are to be expected, because vasculitis is a lesion found in association with many diseases as yet unrelated in etiology,[21] and because the lesion itself varies from disease syndrome to disease syndrome. It is this variable nature of the lesion

that has obliged us to classify it as a "polyvasculitis" rather than as a "periarteritis nodosa."

In addition to the commonly accepted sulfonamide lesions discussed above, we have encountered two unusual lesions, a granulomatous reaction and a splenic trabeculitis, that we attribute to sulfonamide medication. These peculiar granulomata are the lesions most frequently found in our series, but they have been described only recently by others. Evidence that they are sulfonamide lesions is found both in the literature and in our own material. At least 2 cases occurring in man have been described and attributed to sulfonamides,[10, 11] while a similar reaction has been produced in dogs with sulfadiazine.[9] Among our 22 cases, 13 showed granulomatous reactions involving a total of 25 organs. In 11 of these 13 cases sulfonamide lesions of the commonly recognized and accepted types were also found. The only factor common to these patients, aside from the lesions produced, was the administration of sulfonamides. No other possible etiological agent was found in a single case, and a bacterial cause was excluded in all cases by negative post-mortem blood cultures and absence of bacteria from sections of the lesions especially stained to demonstrate their presence. Moreover, the control series contained no examples of lesions similar to these sulfonamide granulomata.

So far as we are aware, the splenic trabecular lesion has not been described in the literature, although Maisel, Kubik, and Ayer [10] have reported a case with vasculitis of the splenic trabecular vein. They attributed this lesion to sulfonamide therapy. Six of our 22 cases showed trabeculitis, and in one of the 6 it was associated with a splenic polyvasculitis. Accepted and recognized sulfonamide lesions were also present in 5 of these 6 cases while the remaining example was associated with a peculiar nephritis that possessed many features of a sulfonamide nephritis. A careful search of the control series failed to reveal a single example of any lesion that resembled the trabeculitis of these 6 cases.

While offering evidence drawn both from the literature and from the present series of cases as support for the sulfonamides as the cause of all of the lesions described above, we are nevertheless aware of the lack of morphological specificity existing in this entire group of lesions. We are of the opinion that many etiological agents are capable of producing lesions similar to those caused by sulfonamides. This is obviously so in the case of the interstitial inflammatory [22, 23] and the necrotizing lesions.[24, 25] For example, in both scarlet fever and diphtheria an interstitial myocarditis may be found, and in the former, interstitial nephritis may occasionally occur; focal necrosis of the liver

is found in typhoid fever and many bacteria, toxins, and chemical poisons produce more or less extensive tissue death. Indeed, in our control series we have found a few examples of lesions of this character, always, however, with a demonstrable etiological agent. While the cause of polyvascular inflammatory lesions is unknown, this lesion is found in many diseases that may or may not be related in etiology and pathogenesis.[21] Although the control series contained no examples of the granulomatous and trabecular lesions, it is apparent that similar lesions might develop from causes other than sulfonamide treatment, such as tuberculosis, tularemia, brucellosis, and rickettsial diseases.

This manifest lack of morphological specificity of the lesions in question compels a careful analysis of each individual case in which such lesions are found before their production by sulfonamides can be established with certainty. However, if such an analysis is undertaken, there is little difficulty in establishing the presence or absence of a causal relationship for the sulfonamides, and we believe that in our own series of 22 cases such an analysis has established beyond doubt that the lesions described were caused by sulfonamide therapy.

Pathogenesis

While we have established the etiological rôle of the sulfonamides for the lesions presented in this study, the pathogenesis is less easily demonstrated. However, we believe that there is adequate evidence to substantiate the hypothesis that they are of an allergic nature.

A review of the many papers dealing with sulfonamide lesions indicates that, as they have become better known, there has been an increasing tendency to regard many of them as allergic phenomena. When the drugs were first introduced, the untoward reactions and the lesions that occurred were held to be of the toxic type.[1, 2] Gradually, it became obvious that dosage and reaction were not closely correlated, and it was accepted that certain patients possessed an idiosyncrasy to the sulfonamides. The appearance of reactions that were obviously of an allergic nature soon indicated that idiosyncrasy alone could not account for all of the reactions and lesions that might follow therapy. Serum sickness, bronchial asthma, and angioneurotic edema exemplified this type of response.[26] Dermatologists were quick to recognize and warn of the sensitizing properties of sulfonamides when applied to the skin.[27] Wedum [28] obtained allergic responses in guinea-pigs, using sulfonamide azoproteins. He found a variable degree of specificity in the immunological results obtained. More recently, Leftwich [29] has developed an intradermal skin test for sulfonamide hypersensitivity, using the serum of patients receiving the homologous sulfonamide. He

also found that cross reactions between the various related drugs occasionally resulted. Park,[30] using the simple chemicals in a modified scratch test for skin sensitivity, found that certain sensitive patients would react to all of the sulfonamides tested, and even to sulfanilic acid and to procaine.

Because of the present tendency to regard many sulfonamide reactions and lesions as an expression of allergy, we have examined our series with a view to testing the validity of this conception. The evidence from this analysis strongly supports the allergic hypothesis. As we have previously detailed, 4 patients had reactions following sulfonamide therapy that were obviously of an allergic nature. These reactions included painful and swollen joints, skin rashes, conjunctivitis, and asthma. It seems significant that the lesions present in these 4 patients included every type encountered by us excepting only massive hepatic necrosis and nephrosis. This co-existence of the majority of sulfonamide lesions and sulfonamide allergy suggests that the lesions may be the morphological expression of a hypersensitivity reaction, and that this is the case whether they occur in patients who do or do not show clinical allergic sulfonamide reactions. Examination of the additional 7 cases that showed untoward clinical reactions not usually considered to be allergic in type discloses that 5 patients (nos. 8, 15, 19, 20, and 22) suffered no unfavorable reactions when first exposed to the drug. Nevertheless, when exposed to the same or a smaller amount of sulfonamide on a later occasion, they exhibited serious reactions within a very short period of time, suggesting that they had become sensitized in the interval. It is also interesting to note that of these 5 patients, 2 died of massive hepatic necrosis, and another of nephrotic anuria in the absence of renal calculi. Hitherto, these latter lesions usually have been considered to be results of toxic damage by sulfonamides. However, it is rather difficult to accept the toxic hypothesis when we consider that these patients did not react unfavorably to their first course of sulfonamide therapy, but did react immediately to a subsequent exposure, developing acute and serious sulfonamide lesions.

Others have recently considered certain sulfonamide lesions found in man as expressions of allergy. Rich [19, 20] has reported 2 cases of periarteritis nodosa in patients who had hypersensitivity reactions during sulfonamide therapy, and he has considered that the lesions were morphological expressions of hypersensitivity. Recently Black-Schaffer [31] has reported 5 cases of "anaphylactic death" following the administration of sulfonamide drugs. He described varying degrees of arterial damage and interstitial mononuclear cellular infiltrations in

these cases. He considered these lesions to be expressions of allergy and to be comparable to the experimental lesions produced by sensitivity reactions to proteins.

It is true also that many of the lesions that have been described in this paper are comparable to the lesions produced by hypersensitivity reactions to foreign protein in experimental animals. For example, Longcope [32-35] produced interstitial and focal inflammatory reactions in the heart, liver, and kidneys of rabbits, dogs, and guinea-pigs by repeated injections of foreign proteins. The parenchymatous degeneration and predominant mononuclear response of these lesions bear a similarity to the lesions we have found. More recently, Klinge,[36] Vaubel,[37] and Knepper and Waaler [38] have produced arteritis and collagenous and parenchymatous degeneration in sensitized rabbits by repeated injections of foreign protein. More striking, however, was their production of unequivocal granulomata in skeletal and heart muscle and in collagenous tissue, centering on blood vessels. Fundamentally these lesions consisted of focal degeneration of the tissues involved with a histocytic monocytic response. Working with monkeys in somewhat similar experiments, Ferraro [39] has obtained vasculitis and granulomatous formation in the central nervous system.

Rich [19, 20] and Rich and Gregory [40] have ascribed experimental and clinical periarteritis nodosa to hypersensitivity to foreign protein and/or sulfonamide, and have concluded that periarteritis nodosa may be an expression of allergy caused by widely differing antigens. Their work provides additional confirmation for the allergic nature of the polyvasculitis we have described. Of more interest is their experimental production of foci of collagenous necrosis and mononuclear cellular infiltration in the heart by hypersensitivity reactions to foreign protein.[41] This lesion is strictly comparable to the collagenous necrosis and cellular infiltration of the trabeculae of the spleens in 6 of our cases. Clark and Kaplan [42] have also described necrotizing arteritis and periarteritis in small coronary arteries, as well as subendocardial proliferations of histiocytes in the hearts of 2 patients who died while suffering from serum disease. They interpreted these lesions as expressions of hyperergy following the administration of foreign serum.

In presenting the above discussion we have sought to show that there is ample justification for the conception of the allergic nature of the sulfonamide lesions. It has been noted that various investigators have demonstrated that the sulfonamides can produce immunological reactions *in vivo*. The occurrence of significant allergic manifestations, both in the present series of cases and in the cases of sulfonamide lesions that others have reported, has been discussed, and an attempt

has been made to show that an acceptable degree of morphological similarity exists between the lesions produced by hypersensitivity to foreign protein and those attributable to sulfonamides. We conclude, therefore, that the lesions reported in this paper are based upon sulfonamide hypersensitization.

The fundamental pathological change that is elicited by the allergic reaction is not apparent in the material of this series. There is no evidence that any single tissue is the primary reactant. Basically, all of the lesions we have examined are a complex of tissue destruction and of proliferation of the reticulo-endothelial cells in the affected area. For example, the infiltration and the granulomata of the heart seem to be fundamentally an expression of the destruction of tissue with an associated mononuclear cell response. Similarly, in the liver the areas of early necrosis with a minimal or moderate mononuclear cell response seem to be merely the initial stages in the development of the mature granuloma in which none of the original parenchyma remains. Furthermore, the massive hepatic necrosis and the case of nephrosis appear to be examples of massive parenchymatous destruction resulting in death before a mononuclear cell response is apparent. But, it is to be remembered that the preservation of the Kupffer cells in the midst of extensive hepatic necrosis, and the prominent reticulo-endothelial proliferation found in all lesions, suggest that while degeneration and necrosis are the earliest observable morphological changes, they are not necessarily the fundamental ones. We cannot determine, therefore, whether necrosis or reticulo-endothelial activity is cause or effect of the reaction, but, regardless of the varying proportions found between these two elements, it is our conviction that all of the sulfonamide lesions described are fundamentally the same, differing only in the phase and intensity of the reaction.

Whatever the fundamental reaction elicited by the allergy may be, it is impossible to say exactly what factors permit its development in some persons and not in others. In most of the cases in the present series the patients were suffering from an illness, more or less serious, before sulfonamide drugs were given. There is some evidence to suggest that altered metabolism from disease or nutritional deficiency may play an important rôle in the development of sulfonamide sensitivity. This probability is borne out by a recent study in which 5,000 healthy men received sulfadiazine prophylactically with negligible untoward effects.[43]

Summary and Conclusions

Examination of 375 autopsies of patients who had received sulfonamides revealed 22 cases with lesions attributable to sulfonamide medication. These lesions were regarded as severe enough to cause

death in 7 cases, were major factors contributing to death in 7 additional cases, and were apparently of negligible importance in the remaining 8 cases. No statistical interpretation of these figures is possible. Among these 22 cases examples of the majority of the commonly reported sulfonamide lesions were found. In addition to these, however, a granulomatous reaction that has been reported but rarely was found to be the lesion of highest incidence, occurring in 13 cases. A unique lesion, a splenic trabecular necrosis and inflammation, was found in 6 cases. The evidence that these latter lesions were caused by sulfonamide therapy consists of the lack of other demonstrable causes, their co-existence with recognized sulfonamide lesions and, in the case of the granulomata, their experimental production with sulfadiazine. It was found that all lesions invariably combined necrosis of the tissues involved with activity of the reticulo-endothelial system. This basic similarity of the structural alterations indicated a fundamental pathogenesis common to all of the lesions. The association of all types of lesions described with clinical evidence of sulfonamide hypersensitivity, and the essential identity of these lesions with those produced in animals, by various investigators, by foreign protein sensitization, led to the conclusion that the lesions were always an expression of allergy.

While this report is obviously of some interest to the clinician and therapist, we believe that its chief value lies in its relation to the general problem of the pathology of allergy in man, an important and, as yet, relatively unexplored field.

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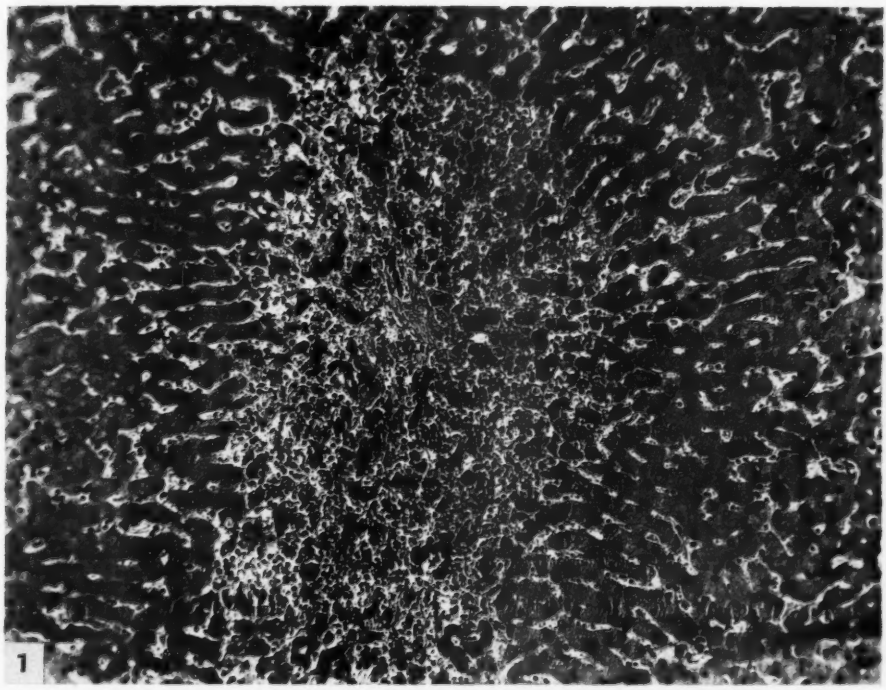
[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 138

FIG. 1. Case 9, liver. An area of recent central necrosis with disruption of the liver cords is seen. An interstitial infiltration of inflammatory cells which are predominantly mononuclear accompanies the necrotizing reaction. The liver cells bordering the immediate area of necrosis show severe degeneration, while those that are slightly removed show only cloudy swelling. Hematoxylin and eosin stain. × 137.

FIG. 2. Case 16, liver. Many areas of focal necrosis similar to the one in this field were found in this liver, which also contained mature granulomatous lesions. The size and shape of the lesion, in addition to the appearance of the liver cells, suggest that this lesion is the precursor of the typical granulomatous reaction (Figs. 3 and 4). It is to be noted that the characteristic cellular reaction of the granuloma can be identified in this lesion, but that it is minimal. Hematoxylin and eosin stain. × 310.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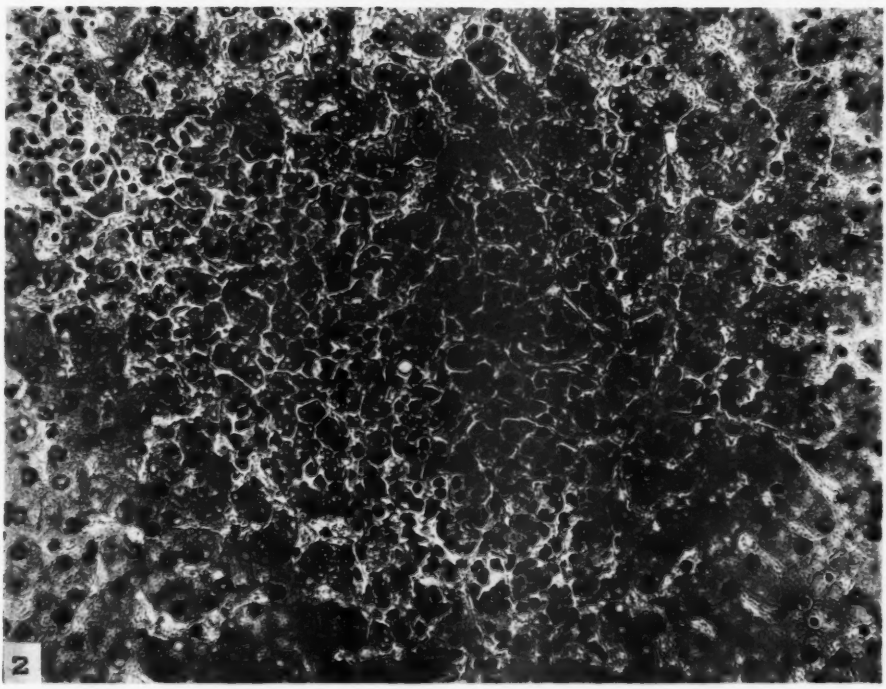
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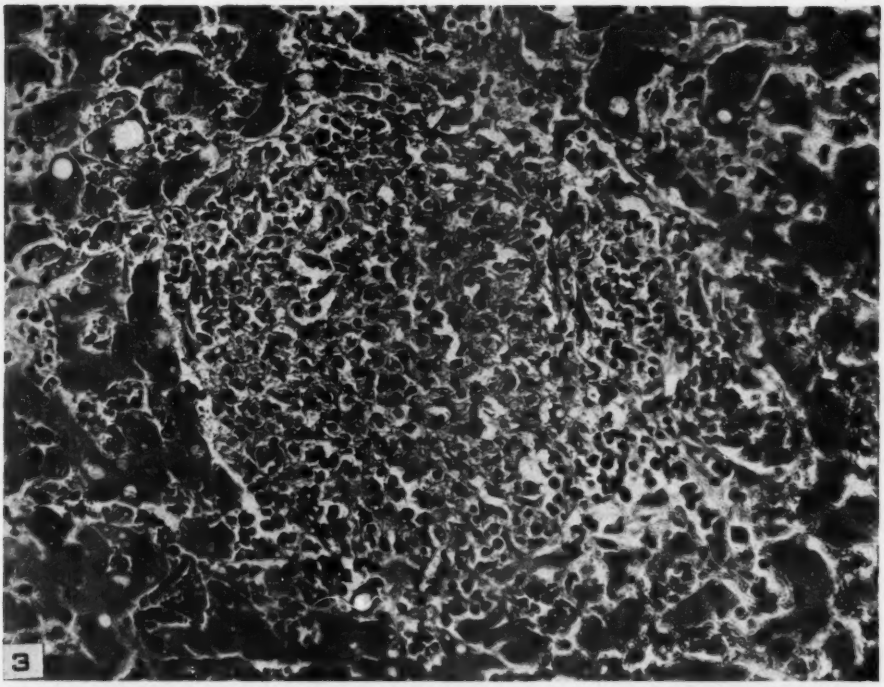
PLATE 139

FIG. 3. Case 21, liver. A moderately mature granuloma of the liver is seen to show very few identifiable liver cells among the cells of the monocytic reaction. Plasmatoid and polymorphonuclear leukocytes are present in small numbers. (See also Figs. 5 and 6 from the same patient.) Hematoxylin and eosin stain. × 260.

FIG. 4. Case 14, liver. At a high magnification, a mature granuloma of the liver shows the characteristic tessellated appearance of the lesion. The predominantly monocytic nature of the cellular reaction and the blurred eosinophilic interstitial material can be identified. No liver cells are found in this lesion. The lesion is clearly demarcated from the neighboring liver cells. Hematoxylin and eosin stain. × 415.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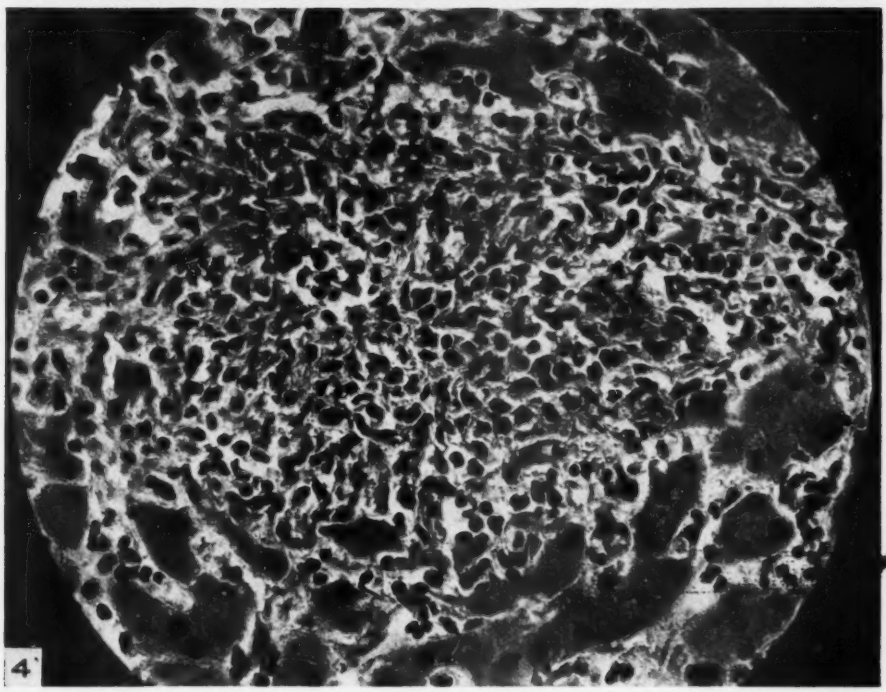
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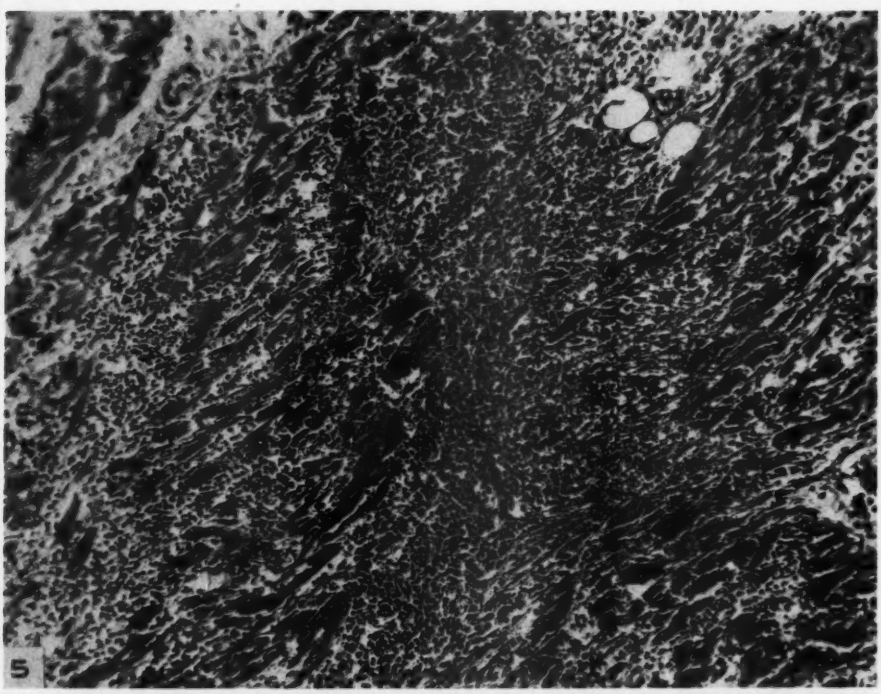
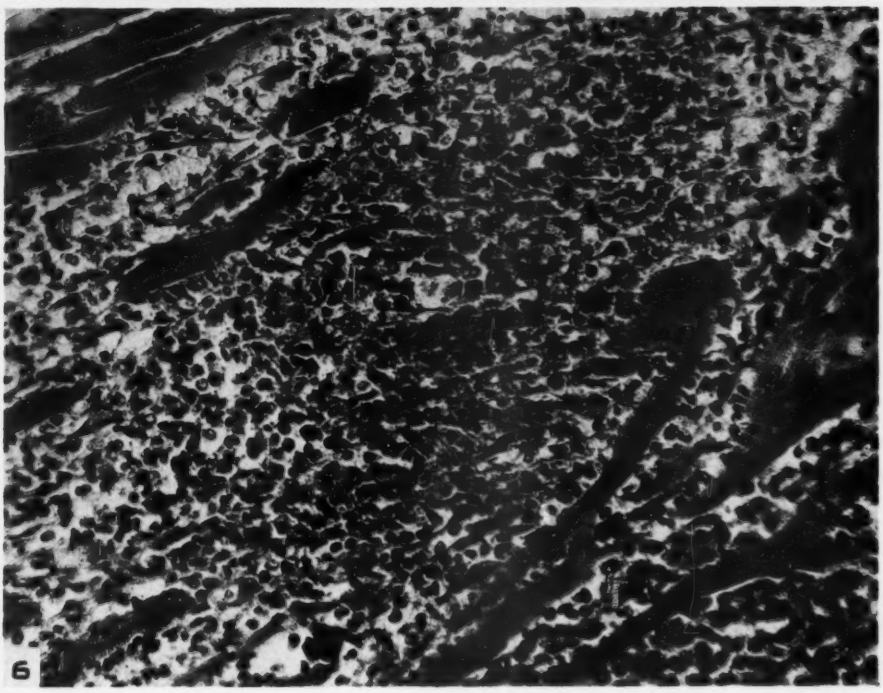
PLATE 140

FIG. 5. Case 21, heart. At a low magnification, a lesion from the same section of heart muscle as Figure 6 shows a rather mature and widespread granulomatous lesion. The same features that may be noted in Figure 6 are present, with the addition of an extensive associated interstitial myocarditis. Lesions of this extent were numerous in all parts of the myocardium in this case. (See also Figs. 3 and 6 from the same patient.) Hematoxylin and eosin stain. × 124.

FIG. 6. Case 21, heart. A moderately mature granulomatous focus is seen lying in the heart muscle. The muscle fibers close to the lesion show necrosis of a Zenker's type. The sharply demarcated nature of the muscle destruction is striking. The cellular content of the granuloma is of a rather uniform mononuclear type, but plasmatoid and polymorphonuclear cells are numerous. (See also Figs. 3 and 5 from the same patient.) Hematoxylin and eosin stain. × 314.





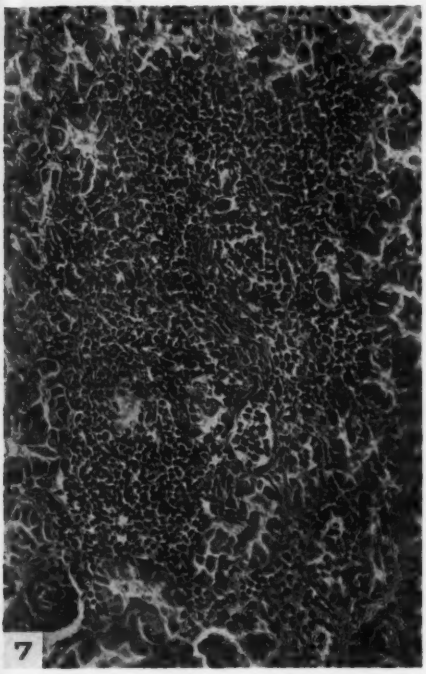
More, McMillan, and Duff Sulfonamide Allergy in Man

Plate 141

Fig. 7. Case 12, kidney. A mature granuloma with rather ill-defined limits is seen surrounding necrotic, but still recognizable, renal tubules. There is a slight interstitial nephritis. Hematoxylin and eosin stain. × 150.

Fig. 8. Case 15, spleen. A swollen, ragged and frayed splenic trabecula is seen. It stains poorly and its few nuclei are pyknotic. It is heavily infiltrated with inflammatory cells, some of which form abscess-like foci at the border between the pulp and the trabecula. (See also Fig. 10 from the same patient.) Hematoxylin and eosin stain. × 106.

Fig. 9. Case 13, kidney. Peritubular granulomatous foci are seen about the collecting tubules near the tip of a renal pyramid. Necrotic tubular epithelium can be identified with difficulty. Hyaline casts and a multinucleated, crescentic giant cell are to be noted. Hematoxylin and eosin stain. × 144.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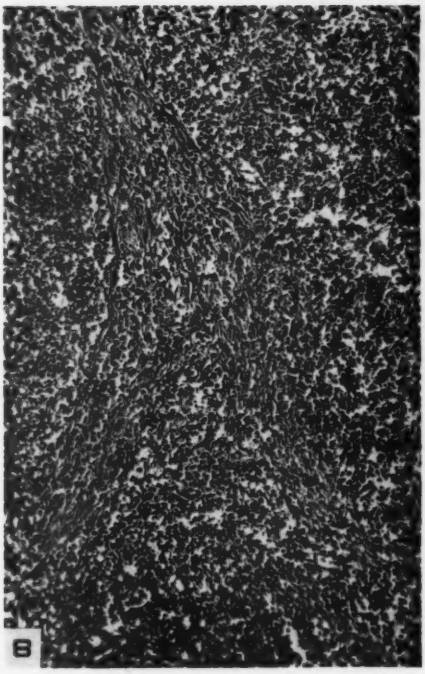
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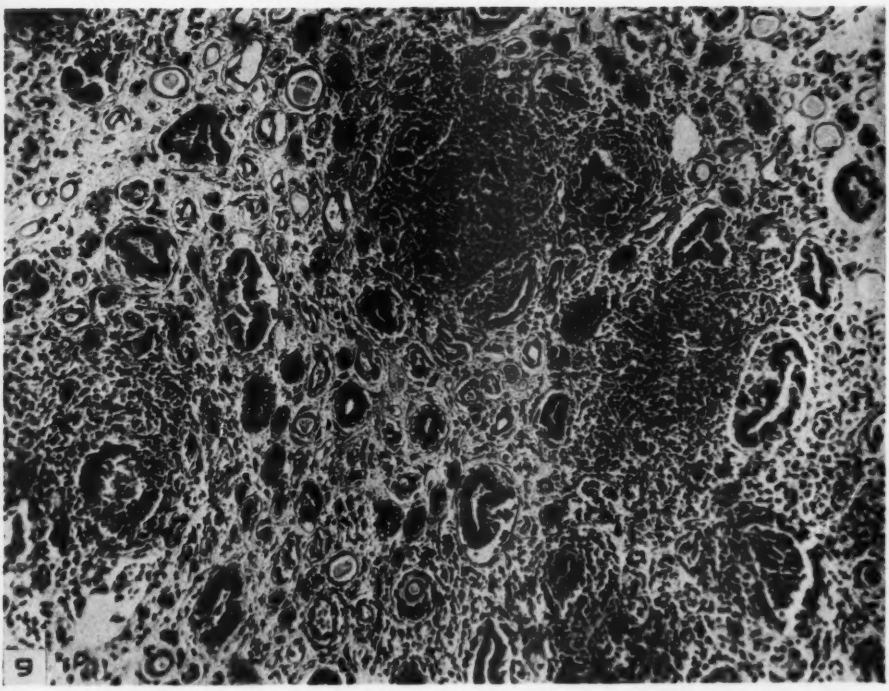
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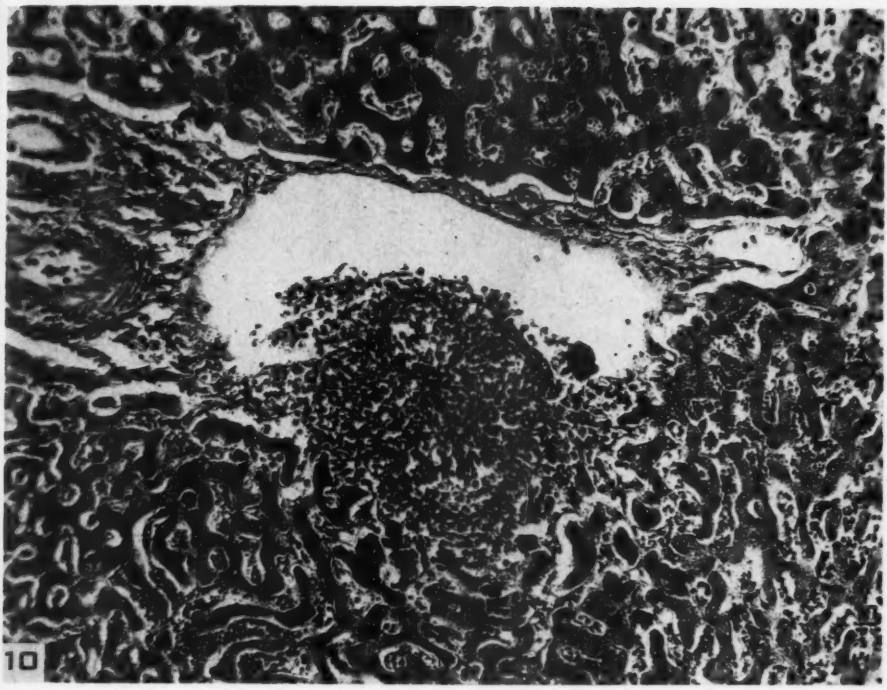
PLATE 142

FIG. 10. Case 15, liver. A rather acute granulomatous reaction is seen involving a portal area. The lesion has an explosive appearance. There is destruction of a segment of the wall of a portal vessel and the lesion contains fragments of material that suggest fibrinoid necrosis of collagen. The general liver parenchyma shows engorgement and cloudy swelling. (See also Fig. 8 from the same patient.) Hematoxylin and eosin stain. × 146.

FIG. 11. Case 4, spleen. There is vasculitis of a medium-sized trabecular artery. It shows complete destruction with fibrinoid necrosis of the media, and plugging of the lumen with desquamated, proliferating intimal cells. The adventitia is infiltrated with mononuclear cells admixed with substantial numbers of polymorphonuclear leukocytes and small round cells. The cellular reaction extends into the trabecula. Hematoxylin and eosin stain. × 340.

FIG. 12. Case 17, pelvis of ureter. Vasculitis affecting a small artery and vein is seen. The musculature of the artery is smudgy, necrotic, and eosinophilic in staining reaction. It possesses no nuclei. The adventitia and periadventitia are infiltrated with small round cells and polymorphonuclear leukocytes. Hematoxylin and eosin stain. × 160.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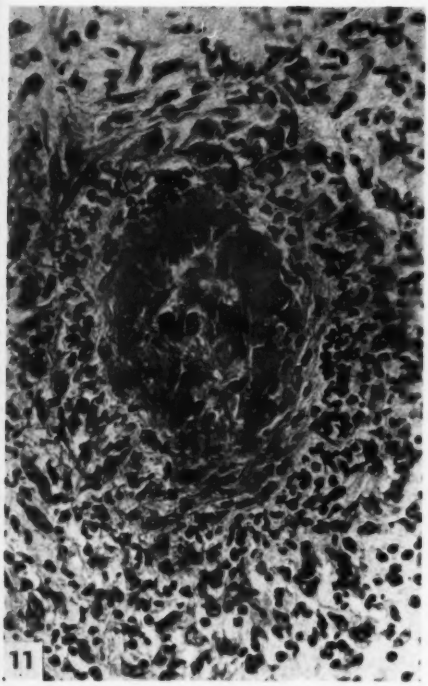
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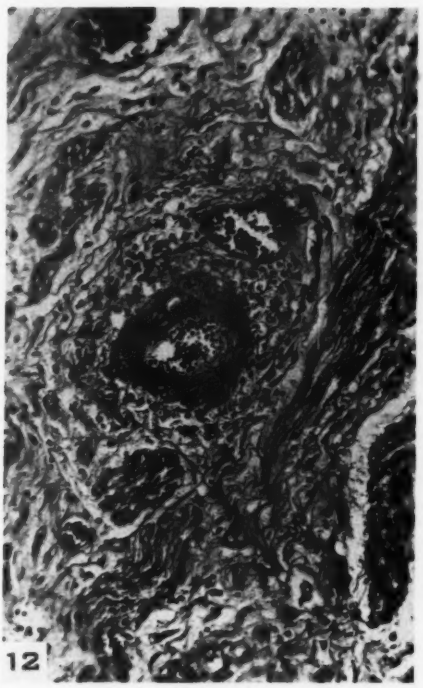
12

EXPERIMENTS WITH JAAGSIEKTE*

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In 1933, a disease of sheep was introduced into Iceland from Germany which has caused enormous losses to the farmers, who in some places have lost 60 per cent and even more of the stock during a couple of years, as mentioned in a previous publication.[1] The identification of this disease with jaagsiekte, as described by Cowdry [2,3] and Cowdry and Marsh,[4] Mitchell,[5] and de Kock,[6,7] seems to be justified, as described by me [8,9] in previous publications. As symptoms and pathological changes have been described in the publications already referred to, I shall only repeat here what is necessary for a better understanding of my experimental work.

The characteristic *symptoms* are a slowly increasing dyspnea accompanied by excretion of frothy, slightly opalescent, watery mucus from the respiratory passages. The beginning of the disease is insidious and 6 months usually pass from the time of contact until visible symptoms appear. There is no elevation of temperature. The most reliable clinical test in suspected cases is to turn the sheep with head downwards and notice whether watery fluid drips from the nose. If it does it is a reliable symptom, which has never failed in diagnosing this disease. On the other hand, this secretion may be absent in the initial stage and also in the late stages of very chronic cases, in which fibrosis has superseded the specific changes.

PATHOLOGICAL CHANGES

The initial changes, which are strictly limited to the lungs, consist of tiny grayish spots, just visible to the naked eye, which soon tend to become confluent. In sections they appear with low magnification (Figs. 1 and 2) as dispersed, darker colored spots of varying size, some being tiny tufts, others displaying distinct adenomatous characteristics. Some can be traced to bronchial epithelium (Fig. 3), others to the alveolar lining (Fig. 4).

A constant feature is a more or less pronounced cellular exudate in the alveoli, consisting chiefly of mononuclear cells, which are derived at least partly from the lining epithelium, but segmented neutrophilic leukocytes are frequently seen (Fig. 3) and red blood corpuscles are often conspicuous. In rare cases a pronounced lymphoid hyperplasia may be observed (Fig. 5). In some cases intrabronchial proliferation is very pronounced (Figs. 5 and 6), but is always limited to the

* Received for publication, July 14, 1945.

bronchioles. I have never observed any growth in the bronchi visible to the naked eye.

The structure of the epithelium is, as a rule, very regular and of the type of a benign adenoma (Figs. 7 and 8), but in exceptional cases the structure may assume a more irregular aspect (Fig. 9), suggesting malignant growth. Yet I have never seen metastatic growth in the tracheobronchial glands or elsewhere.

In advanced cases the lungs become greatly enlarged (Fig. 10), mottled grayish blue (Fig. 11), smooth and tense. A frothy watery liquid oozes from the cut surface, displaying a nodular, friable, light grayish tissue (Fig. 12) from which a viscid grayish mucus exudes on pressure, not unlike "cancer milk" except that it is gray instead of white. The edematous accumulation in the lungs is sometimes enormous, and when the lungs are enlarged and distended with liquid the increase in weight may be pronounced. Frequently I have seen lungs weighing 2500 to 3000 gm. the pair, whereas normal lungs rarely weigh more than 400 gm. A pronounced hypertrophy of the heart may be present in such cases, but as a rule it is not conspicuous. Sudden death is sometimes observed as a consequence of increased exertion, as, for instance, when a sick sheep is made to run; but usually terminal pneumonia leads to death.

Experiments

In spite of innumerable attempts to cultivate the causative organism, all such attempts have failed. As a rule no growth has been observed. Various strains of streptococci, which were isolated from many cases and injected into healthy sheep, evidently bore no etiological relationship to the disease.

Small pieces of tissue, up to pea size, cut with sterile precautions from the specific tissue and put directly into broth, gave no growth after a week's incubation in some cases where contaminating organisms were not present.

A natural infection has never been observed in cattle, although sick sheep have frequently been housed in cow stalls. Goats have not been affected on the few farms where they were kept with sick sheep. Neither have we ever encountered such a disease in man in our autopsies, and there is no case on record in this country which suggests a possible transfer of jaagsiekte to man.

Experimental inoculations were made on mice, guinea-pigs, and rabbits, but all without any positive results. I therefore limited my experimental inoculations to sheep as the only animals susceptible to this disease. Previous experiments [8] had shown that the disease can easily

be transmitted by housing healthy sheep with sick ones. When sheep were housed together, several means of transmission were possible: (1) through feces or urine, (2) through external parasites, (3) through bronchial secretion dispersed in the respiratory air.

1. Three lambs were fed by stomach tube with feces from a sick sheep. After 8 months they were killed, and no traces of adenomatosis were found nor any particular changes in the lungs.

2. The possibility that the wool-louse, *Melophagus ovinus*, might convey the virus was considered, and for that purpose a great number of melophagi from sick sheep were transferred to 5 healthy lambs. These lambs were killed after 8 to 10 months, with negative result.

In order to exclude any possibility of infection except the respiratory air, the following experiment was made:

Two healthy young sheep were confined (March 18, 1941) with a sick sheep in a small compartment in such a way that the head and neck of the sick sheep were directed to the outside through a hole in the wall. The rim of the hole was padded, so that no current of air could pass through. In this way the whole body of the sick sheep, with the exception of the head, was in contact with the healthy sheep which, in the narrow compartment, turned their heads in the opposite direction. An infection might be supposed to take place if any external parasite or fecal material were contagious. The sick sheep was held in this position for 14 days, when it was taken away by removing the wall. The 2 healthy lambs were kept for a month afterwards in the same compartment and then taken to another compartment where they had more space. Four and a half months later one of the lambs died suddenly of pneumonia. Autopsy showed no sign of jaagsiekte. The other lamb remained healthy and showed no signs of jaagsiekte when killed 7 months after the start of the experiment.

3. The previous experiments having pointed to an exclusion of all but the respiratory factor, the following experiments were made:

Two lambs were put in an elevated compartment 1.5 yards above the head of a sick sheep kept in a lower compartment. Strict precautions were taken that no material particles and nothing except the air could move from the lower to the upper compartment. This experiment was repeated three times, each trial lasting 4 to 6 months. Of 8 lambs used in these experiments, 3 contracted typical jaagsiekte, but 5 showed no signs of the disease.

A further attempt to demonstrate the respiratory transmission of the disease was the following:

On January 28, 1941, a sick sheep was made to breathe through a 20 per cent solution of glycerine in saline water for 30 minutes. This

breathing was made possible by employing a specially constructed mask with two valves, one for expiration and one for inspiration, the expiratory valve being connected with rubber tubing to the bottom of a jar containing the glycerine mixture. After the sheep had breathed through this mixture, the slightly opalescent fluid was injected, 5 cc. intratracheally and 2 cc. intrapulmonally on the right side, into each of 3 lambs. Two lambs developed typical jaagsiekte, one of them (no. 873) showing clinical symptoms 4 months later when extensive typical lesions were found. In the other (no. 872) a small pea-sized nodule was found in the middle lobe of the right lung, histologically typical adenomatous jaagsiekte. This node was cut in serial sections in its entirety and every other section examined. No worms, eggs, or larvae could be found in it or its vicinity.

When lamb 873 showed unmistakable symptoms of jaagsiekte, it was made to breathe through a glycerine-saline solution as described. This fluid was filtered through a gradocol membrane with pores 0.9 μ in diameter. While the filtration was taking place the lamb was killed to corroborate the clinical diagnosis. A frozen section showed a typical histological picture of jaagsiekte. Two cc. of this filtrate was injected into the right lung of each of 4 lambs on May 28, 1941. Four months later (September 20, 1941) one of these lambs showed symptoms of jaagsiekte. It was killed and both lungs were found to be affected. The main lesion was located in the right apical lobe, half of which was partly indurated, partly soft and friable, light gray and nodulous, macroscopically typical of jaagsiekte. Histologically the lesions were also typical: papillomatous adenomatous lesions with surrounding mononuclear alveolar exudation. No bacteria were visible in direct preparations. The other 3 lambs were killed later on the same day. In the right lung of one of them (no. 877) a chronic pneumonia was found as an area of slight consolidation on the posterior part of the posterior lobe. Papillary epithelial proliferation was seen in some places, but it was so slight that a positive diagnosis of jaagsiekte was not made. The other 2 lambs were normal.

Parallel with the first experiment, started January 28, 1941, another was begun with the filtered expiratory fluid. The filtration was done through a 0.9 μ gradocol membrane. Of this filtrate, 5 cc. was injected intratracheally into each of 4 lambs.

Four months later (May 26) one of these lambs, which, as always, were kept isolated from other sheep, was suspiciously dyspneic. It was killed the following day and the autopsy showed a typical picture of jaagsiekte in both lungs. The whole apical lobe was consolidated, fairly dense in the upper half, but soft, friable and almost gelatinous in the

lower portion where the process was in progress. In the right lower lobe typical scattered lesions were found. The left lung also showed fairly extensive lesions with friable, soft tissue. Histologically these lesions were typically adenomatous. The other 3 lambs were killed on the same day, and none of them were found affected.

Experiments with Filtered and Unfiltered Material from Affected Lungs

Experimental inoculations with filtered and unfiltered tissue were very discouraging. As we had before our eyes the constant spread of the disease among the flocks, I was surprised at the negative results with inoculations of affected lung tissue. These experiments were conducted along the same principal lines: Typical jaagsiekte-lung tissue from freshly discovered cases was ground with sterile sand in a mortar with saline solution. This was filtered through eight layers of gauze and injected directly when unfiltered material was used, or filtered through Chamberland, Berkefeld, or Seitz filters or gradocol membranes when filtered material was used.

Tables I to III give a survey of these experiments.

Experiments with Collodion Sacs

After a preliminary study, it was found easy to make transpleural operations on lambs for the purpose of inserting material into their lungs. Under ether narcosis a rib was resected and the incision in the pleura plugged immediately by pulling the lung tissue outwards through the wound to prevent pneumothorax. In this way small collodion sacs

TABLE I

Experiments with Unfiltered Material

Experiment started	Mode of injection	Duration of experiment	Results	
			Positive	Negative
		(*months*)		
March 6, 1937	Injected intrapulmonally into 3 lambs	7½	1	2
May 3, 1937	Injected intrapulmonally into 3 lambs	7½	1	2
Nov. 12, 1937	Injected subcutaneously into 2 lambs	6	0	2
May 4, 1938	Injected intrapulmonally into 5 lambs	6	0	5
Oct. 3, 1938	Injected intravenously into 3 lambs	3	0	3
Nov. 18, 1938	Injected intrapulmonally into 5 lambs	2–3	0	5
Sept. 16, 1939	Injected intrapulmonally into 3 lambs	2–8	0	3
April–May, 1939	Injected intrapulmonally into 5 lambs	3–4	0	5
Sept. 22, 1939	Injected intrapulmonally into 3 lambs	2–9	0	3
Sept. 16, 1939	Sprayed into nostrils of 3 lambs	2–8	0	3
Jan. 26, 1940	Injected trypsin-digested, unfiltered tissue into 3 lambs, also sprayed into nostrils	6	0	3
Totals			2	36

containing finely minced jaagsiekte-lung tissue could be inserted into the lung, whereupon the incision in the lung was sutured and the pleural wound closed. After the skin wound had been sutured and the lambs awakened from their narcosis, they were brisk and walked about as before.

On January 4, 1939, 5 lambs (nos. 700 to 704) were operated upon in this way, one collodion sac with jaagsiekte tissue being inserted into

TABLE II

Experiments with Filtered Material

Experiment started	Filter employed	Mode of injection	Number of lambs	Duration of experiment	Results	
					Positive	Negative
				(*months*)		
1937:						
March 11	Seitz E. K.	Intrapulmonal	5	7½	0	5
Nov. 12	Seitz E. K.	Intrapleural (1 died 2 weeks later from intercurrent infection)	2	8½	1	1
Nov. 12	Chamberland L 2	Intrapleural	2	8½	1	1
Nov. 12	Seitz E. K.	Subcutaneous	3	8½	2	1
1938:						
May 4	Berkefeld-N.	Intrapulmonal	5	5	1	4
Sept. 5	Seitz E. K.	Subcutaneous	10	½–3½*	0	10
Sept. 15	Seitz E. K.	Intrapulmonal	10	½–4½*	0	10
Oct. 3	Seitz E. K.	Intravenous	10	4	0	10
Oct. 3	Seitz E. K.	Intrapulmonal	5	4	0	5
1939:						
Sept. 16	Chamberland L 2	Intrapulmonal	3	7	1	2
Sept. 16	Chamberland L 2	Sprayed into nostrils	3	4–9	0	3
Sept. 22	Chamberland L 2	Intrapulmonal	3	8	0	3
1940:						
Aug. 23	Chamberland L 2	Intrapulmonal	3	8	0	3
Totals			64		6	58

* These lambs began to die from diarrhea 2 weeks after the experiment was started.

the right lung of each. From January 10, lamb 701 was dyspneic, with fever, and it was killed on January 16. An extensive pneumonia was found in both lungs, but nothing resembling jaagsiekte. The operative wound was found completely healed with no reaction around it. The pneumonia was found to be caused by the bacillus of contagious pneumonia, yielding unusually hemolytic colonies.

On January 28, lamb 700 was killed, after showing conspicuous dyspnea. Nothing was found at autopsy except a slight atelectasis about the sac, around which a whitish fibrous capsule had formed. Nothing resembling jaagsiekte was found macroscopically or microscopically.

On March 4, lamb 702 was killed. No changes were found in the lungs.

No. 703 was killed on May 13, almost 4 months after insertion of the sac, without having shown any suspicious symptoms. The lungs were of normal size and displayed no outward abnormality. The collodion sac was found intact, but hardened and embedded in a fibrous capsule. Around this capsule was a patchy tissue, 1 to 1.5 cm. in thickness, with grayish nodules, greatly resembling jaagsiekte. Histologically this tissue was found to be typical adenomatous jaagsiekte.

No. 704 was killed on April 11 and nothing abnormal found.

TABLE III

Experiments with Injection of Bronchial Secretion

Experiment started	Mode of injection	Number of animals	Duration of experiment (*months*)	Results	
				Positive	Negative
	Unfiltered material				
Sept. 8, 1937	Sprayed into nostrils	2	4½–7	0	2
April 30, 1937	Intratracheal	5	3½	0	5
Oct. 3, 1938	Intrapulmonal, directly from a sick sheep	3	3½	0	3
Oct. 3, 1938	Intratracheal, directly from a sick sheep	2	3½	0	2
	Totals	12		0	12
	Filtered material				
Sept. 6, 1937	Chamberland L 3, sprayed into nostrils	2	8	1	1
April 30, 1938	Berkefeld-N, intratracheally	5	4	0	5
	Totals	7		1	6

Of the 5 lambs in this experiment, only one developed jaagsiekte, but it must be remembered that 2 of the lambs died within a month of the inoculation and the other 2 were killed rather early, within 3 months after the inoculation.

Transfusion Experiments

Between January 5 and 10, 1939, blood was transferred into 4 lambs from sick sheep, from 50 to 700 cc. into each in a single session. These lambs were killed after 6 months, none of them displaying any signs of jaagsiekte.

WORMS AND JAAGSIEKTE

The causative relationship between lung worms and jaagsiekte has been discussed by M'Fadyean [10] and by me,[1,9] both reaching the same conclusion, *viz.*, that lung worms are not directly responsible for the

disease. One of my experiments, in which a lamb was brought up under worm-free conditions and yet contracted the disease, apparently through air-borne infection, points to a direct transmission without any interaction of worms. Serial sections of primary nodules have in some cases revealed Muellerius larvae, but in others, none.

On the other hand, when the difficulty of direct transmission was realized, I could not reject the possibility of some intermediary agent. Since every sheep in this country is infected with the lung worm, *Muellerius capillaris*, and this worm is as strictly limited to sheep as is jaagsiekte, no other animal being susceptible to Muellerius, we thought that this parasite might possibly be an intermediary host to the virus, possibly in a similar way to that which Shope [11] has found for lung worms of hogs and rain worms which harbor the virus of swine influenza, and Syverton and Berry [12] for the woodtick as transmitter of equine encephalomyelitis. The following experiments were made with this possibility in mind.

The first experiment was made with larvae from jaagsiekte lungs, in order to see whether they might harbor the virus. When that experiment was negative, I thought that the lung worms might "prepare the soil," eventually weaken the tissue, and lower its resistance against the attack of the virus. With the possibility in mind that the sexual hormones of the worms might enter into this combination, perhaps by stimulating epithelial growth, I thought that the alveolar linings might be less resistant in the immediate vicinity of developing worms and therefore more susceptible to contact with the virus when the worms were reaching full development.

The larvae of *Muellerius capillaris*, which are passed by the bronchial secretion into the mouth and from there to the intestinal canal, are found in the feces in variable numbers according to how massive the lung infestation is, but with marked periodic variations as systematic countings have shown. These larvae are eaten by snails, especially land molluscs (*Agriolimax agrestis* and *arion*). I have frequently found the larvae in Agriolimax, of which young specimens are found in abundance in the pastures. I fed young snails (Agriolimax) with Muellerius larvae and kept the snails for 2 to 4 weeks to allow the larvae to develop. Then the snails were fed to lambs, 4 to 8 to each lamb at a time, and this procedure was repeated several times for 2 weeks with each lamb.

Larvae from Jaagsiekte Lungs

In August, 1939, 6 lambs were fed repeatedly with worm-infested snails. A culture of pasteurella-like bacilli of pneumonia [13,14] was repeatedly injected intratracheally during the experimental period. None

of the lambs showed any clinical symptoms of jaagsiekte. Six months later all 6 lambs were killed. No lung changes were found except in one a milium-sized nodule which histologically resembled jaagsiekte, but the picture was not typical.

Larvae from Jaagsiekte-Free Lungs + Filtrate

In parallel with the above experiment, starting at the same time, August, 1939, larvae from jaagsiekte-free lungs were obtained and fed to snails and then to 8 lambs. On November 17, 1939, 3 months after the snails were ingested, a mixture of 4 parts Chamberland L2-filtrate of fresh jaagsiekte tissue and 1 part pasteurella-pneumonia broth-culture, was injected intratracheally, 5 cc. into each lamb. Eight months after the experiment was started all 8 lambs were killed. In 3, typical jaagsiekte lesions were found in the lungs.

It may here be observed that inoculations with the pasteurella-pneumonia organisms were performed repeatedly by various routes, but this organism was never found to produce epithelial proliferations nor anything resembling jaagsiekte when injected alone. Yet its frequent association with the later stages of the disease led me to make numerous experiments with this microorganism, injecting it intratracheally and intrapulmonally into 21 lambs in all and keeping those which did not succumb from the initial pneumonia for 4 to 8 months, with the possibility in mind that the adenomatous proliferation might be a post-infectious process. No trace of epithelial proliferation was found.

IS THE VIRUS INTRAEPITHELIAL?

Intentionally, the findings in direct smears have not been mentioned before in this report. Frequently some bacteria are found, sometimes in great numbers and particularly in cases associated with acute inflammation of the lungs.

In a flock where jaagsiekte is prevalent, some sheep may be attacked suddenly by acute pneumonia, and I usually find then the pasteurella-like bacillus of contagious pneumonia,[13,14] but in other cases hemolytic streptococci may be found. As already mentioned, there is reason to assume that these organisms have no relation to jaagsiekte and must be regarded as concomitants.

One of the most regular findings in smears is to see the protoplasm of a great number of mononuclear cells more or less crowded with vacuoles of a fairly uniform size. These cells are mostly desquamated cells from the alveolar epithelium, but partly also columnar cells from the bronchial tree and the adenomatous tissue. With higher magnification, the protoplasm of these cells is seen to contain minute corpuscles, surrounded by a clear zone. Sometimes a large part of the

protoplasm appears to be filled with these minute corpuscles, as if a great number of them were contained in one large vacuole. The corpuscles themselves are so small that they are just visible at the highest magnification (Fig. 13). No characteristic inclusion bodies have been found. The corpuscles mentioned have been stained with Giemsa's, Paschen's and Castaneda's stains. They are just as distinctly brought out in photomicrographs as by direct examination of stained smears.

One has the impression that these minute corpuscles cause an accumulation of fluid in their immediate surroundings, and that an accumulation of them in a cell will cause an increase in the water content of the protoplasm. If this supposition is right, it might account for the greatly increased water-content in the lungs in these cases and the increased bronchial secretion might be a reaction to the irritative stimulation of the virus particles.

Comment

The cause and nature of jaagsiekte have been problematical, and de Kock,[6] who is one of the most experienced authors on this subject, is inclined to classify this disease among the tumors. The histological picture certainly makes that conclusion probable, and the difficulty encountered by all experimenters might point in the same direction. The problem, however, is not whether the disease should be classified in one category or another but crystallizes around the fundamental question of etiology: What is the cause of jaagsiekte and how is the disease transmitted? I do not pretend to have found a satisfactory answer to this question. Certain facts appear, however, to have been established:

Jaagsiekte is an infectious disease, which is transmitted by the exhaled respiratory air. It is probably caused by a virus, which grows intracellularly in the alveolar and bronchial epithelium. The possibility that the virus may penetrate the placental circulation cannot be rejected, for, although I have never seen the disease in newborn lambs, there are descriptions by reliable persons, from which one can infer that the disease has been observed in lambs 2 weeks old. This, however, seems to occur very rarely. I have never seen the initial stage of the disease in lambs younger than 4 months, which would indicate a postnatal infection. The difficulty in transmitting the disease with unfiltered lung material may be caused by a virus-neutralizing agent in the transferred cells.

Some of my experiments seem to indicate that the disease can be transferred through exhaled air alone. Yet we cannot estimate the possible rôle of lung worms, which are present in every sheep lung in this

country. My experiments indicate that lung worms (*Muellerius capillaris*) are not vectors for the virus. Yet their presence and activity, perhaps in a certain stage of development, may enhance the action of the virus and facilitate its initial development in the alveolar tissue.

Likewise, the bacillus of contagious pneumonia may be of importance in lowering the resistance of the tissue. Although not alone able to cause the disease, it is easier to produce jaagsiekte with a filtrate if it is injected with a culture of this bacillus.

In spite of the difficulty in transmitting the disease, its infectious nature seems to be beyond doubt.

Since no bacteria have been found with any constancy, the assumption of a virus as the infectious agent seems to be the only possible conclusion. The positive results with filtrates tend to confirm that hypothesis. Although cultivation in developing eggs has been unsuccessful (and I have transferred chorionic material from the first inoculated eggs through 8 generations without visible results), that does not exclude the possibility of a virus since it may be, and probably is, one of slow development, as indicated by the long period of incubation.

I am inclined to think that the mononuclear exudative cells are derived from the alveolar lining and that these lining cells may proliferate without losing contact with the alveolar wall, to form an epithelial tuft which may be the beginning of an epithelial growth. Under certain circumstances the nuclei of these cells seem to divide without a corresponding division of their protoplasm, and so giant cells with many nuclei may be formed (Fig. 14). In this respect jaagsiekte would bear a certain resemblance to giant cell pneumonia, as it has been described in children by Hecht,[15] Moore and Gross,[16] Masson and Paré,[17] Karsner and Meyers,[18] and recently by Pinkerton, Smiley, and Anderson.[19] The virus of jaagsiekte might be of plasmodium-like nature, as suggested by Masson and Paré for the giant cell pneumonias, and the minute corpuscles seen in the cells of jaagsiekte lungs somewhat resemble Histoplasma, although of much smaller size. Yet, in contrast with giant cell pneumonias, inclusion bodies are not conspicuous in jaagsiekte.

As already mentioned, I have never seen cases resembling jaagsiekte in man, although we have been looking for it in our autopsy material during the last 8 years. The cases published by Bonne,[20] Bell,[21] and Ikeda [22] of adenomatosis in human lungs resemble jaagsiekte more or less histologically, but since no such cases have been found here, not even among the shepherds, who are in daily contact with sick sheep in closed houses for long periods of time and should have every opportunity of contracting the disease, we must conclude that man is im-

mune to this particular virus. The growth stimulation of this virus is no unique phenomenon, for several irritating substances can cause epithelial proliferation, although only exceptionally to such an extent as the virus of jaagsiekte.

Conclusions

Experimental production of jaagsiekte is bound with great difficulties. There is every reason to conclude that the infectious agent is contained in the expiratory air, and my experiments indicate that the sheep are infected by inhaling the exhaled breath from sick sheep. Experience from this and other countries corroborates this conclusion.

On the other hand, it seems to be practically impossible to convey the infection by means of the watery discharge from the bronchi, which one would expect to contain the virus in great amounts. I have taken this secretion directly from sick sheep and have injected it immediately, warm and unfiltered, into healthy lambs, intrapulmonally and intratracheally, but without result.

Also it seems to be practically impossible to reproduce the disease by injecting unfiltered ground tissue from typical jaagsiekte lungs. Filtered material gave a higher percentage of positive results, but yet the rate of takes was so low that this must be termed a very unreliable method of inoculation. When employed in combination with a broth culture of the bacillus of contagious pneumonia and/or developing lung worms there seemed to be a greater chance of positive results with filtrates. And as both these agents are present in practically every flock and *Muellerius capillaris* is present in every sheep in this country, they might at least in part be responsible for the unusually severe spread of the disease here, although the main cause of the high morbidity rate must be considered to be the housing conditions, for the sheep are kept closely housed for weeks and months under conditions which are ideal for spreading a respiratory infection.

Whether the minute corpuscles reproduced in Figures 13 and 14 are the causal organisms of jaagsiekte I am unable to prove at present. But since these corpuscles are found with greater regularity than anything else resembling organisms I venture to reproduce these photomicrographs as suggestions to investigators.

Summary

Various attempts have been made to reproduce jaagsiekte by inoculating filtered and unfiltered material from affected lungs. Only very few of these gave positive results, particularly with unfiltered material.

Infection was readily brought about by exposing healthy lambs to exhaled air from sick sheep.

Positive results were also obtained by making sick sheep breathe through glycerine-saline solution and then injecting the fluid, unfiltered and filtered, into lambs intratracheally.

Transmission by filtered extracts of tissue proved easier in combination with intratracheal injections of bacillary cultures causing pneumonia in sheep and particularly in sheep which had been fed with snails infested with lung worms of sheep. Yet the lung worm (*Muellerius capillaris*) seems not to be a vector of the virus.

Jaagsiekte is concluded to be due to a pneumotropic virus, strictly limited to the lungs and bronchi of sheep and excreted with the respiratory air.

Photomicrographs are presented of intracellular corpuscles which are tentatively supposed to be virus corpuscles.

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DESCRIPTION OF PLATES

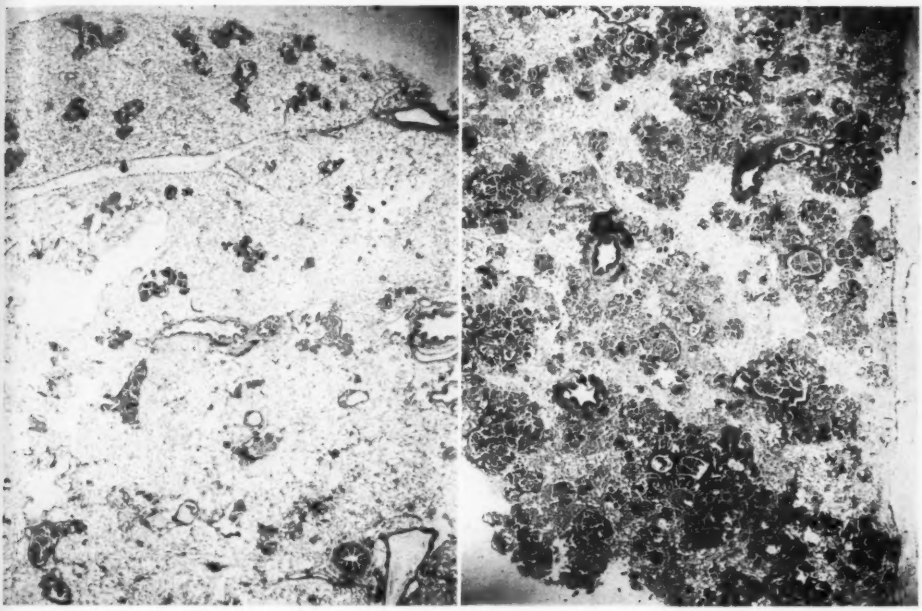
PLATE 143

FIG. 1. Initial lesions of jaagsiekte. × 10.

FIG. 2. Initial lesions with pronounced intrabronchial proliferations. × 10.

FIG. 3. Inflammation and epithelial proliferation in bronchiole. × 280.

FIG. 4. Epithelial tuft originating from alveolar lining. Mononuclear cells in alveoli. × 280.



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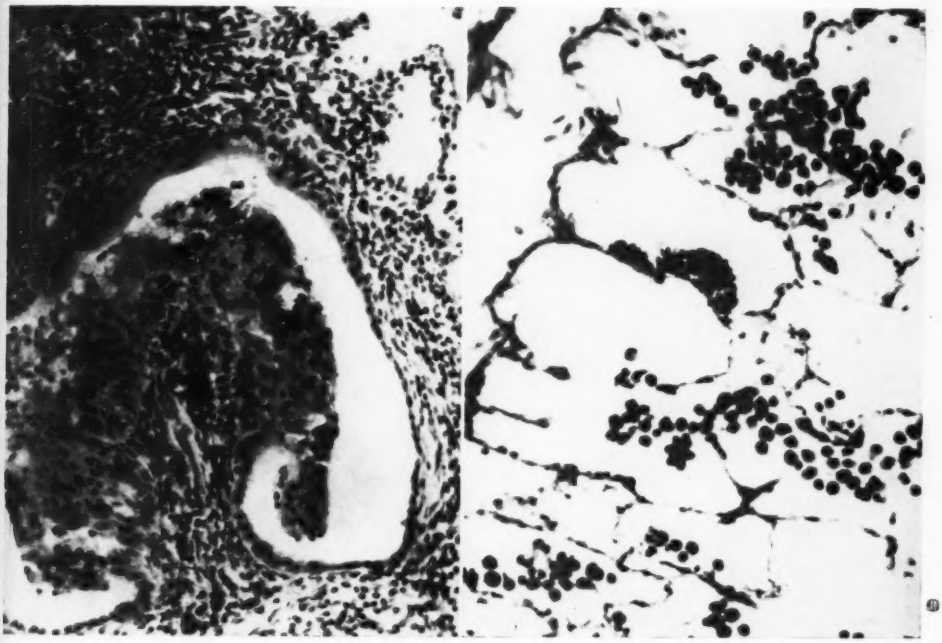


3 4

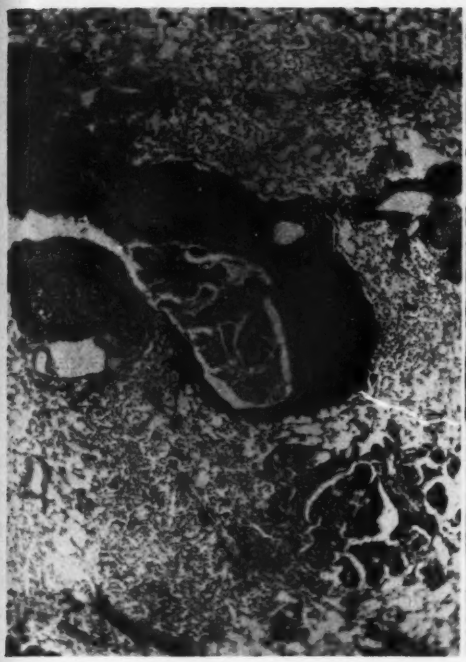
Dungal Experiments with Jaagsiekte

PLATE 144

FIG. 5. Lymphoid hyperplasia surrounding adenomatous proliferation in bronchioles. × 70.

FIG. 6. Intrabronchial adenomatous proliferation. × 260.

FIG. 7. Isolated adenomatous nodule. × 70.



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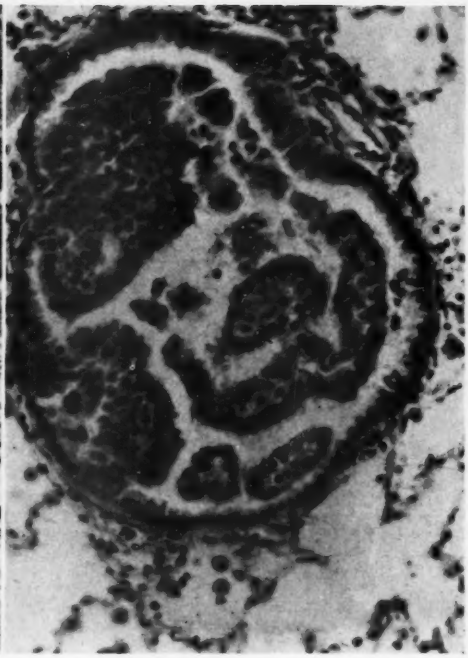

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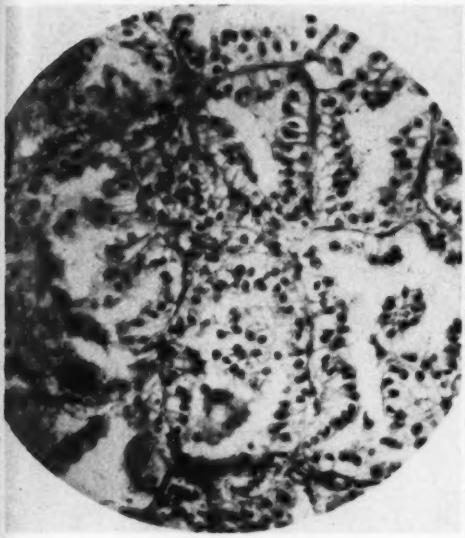
PLATE 145

FIG. 8. Regular columnar cells with clear protoplasm, mounted on delicate fibrous strands. × 240.

FIG. 9. Irregular growth, resembling carcinoma. × 280.

FIG. 10. Advanced case of Icelandic jaagsiekte. A normal lung shown on the right, for comparison.



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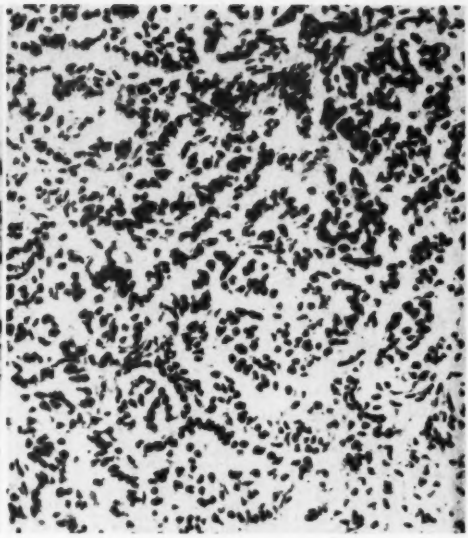

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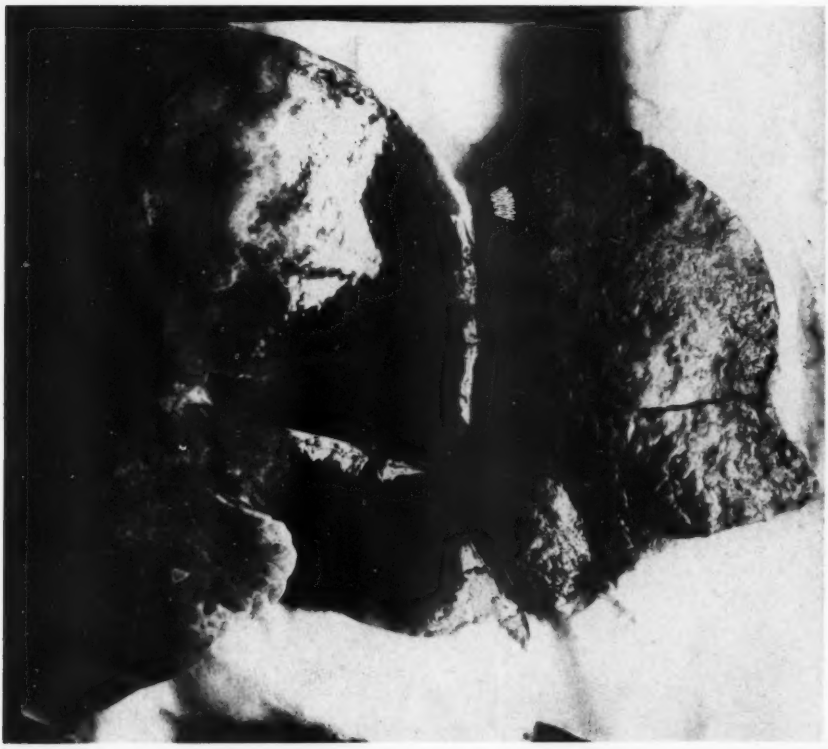
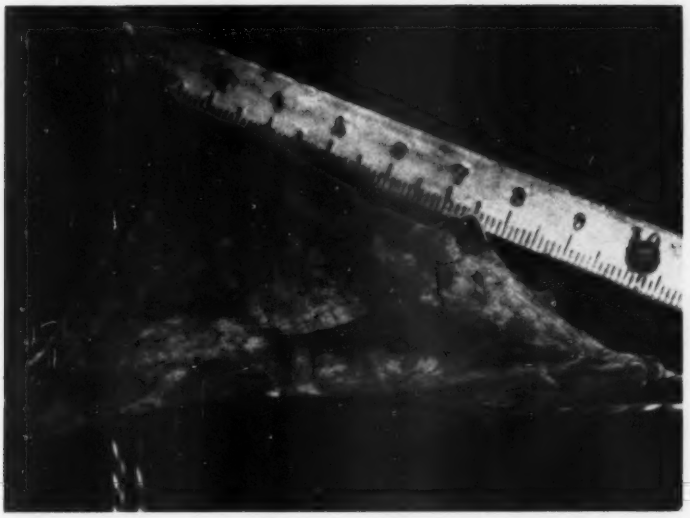


10

PLATE 146

FIG. 11. Mottled surface of adenomatous lung.

FIG. 12. Cut surface of adenomatous lung tissue.



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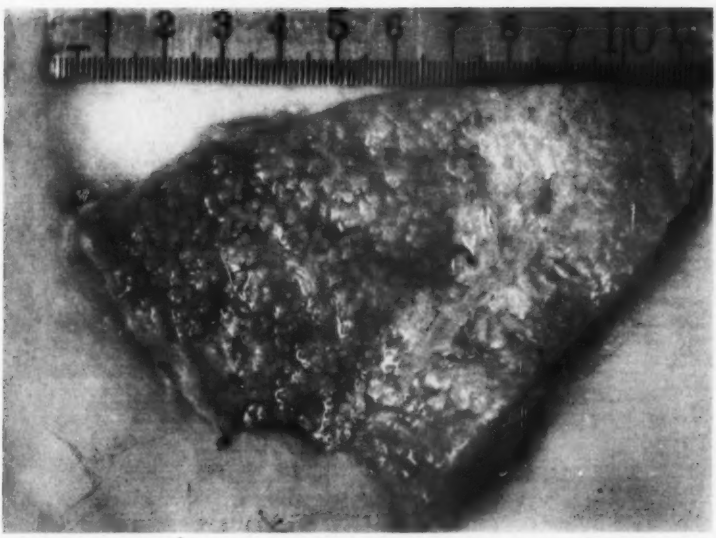


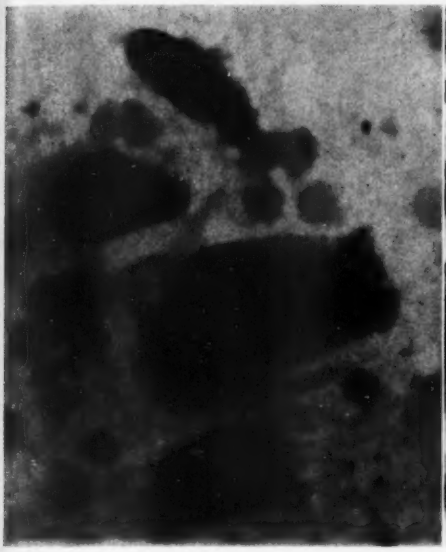
12

PLATE 147

FIG. 13. Intraepithelial virus? Minute corpuscles, each surrounded by a clear zone, in protoplasm of epithelial cell. Giemsa's stain. × 1600.

FIG. 14. Giant cell in section from jaagsiekte lung. Of note are the minute Plasmodium-like corpuscles in protoplasm. × 1600.

FIG. 15. Experimentally produced jaagsiekte, 4 months after injection of 5 cc. of Berkefeld-N filtrate intrapulmonally. × 28.



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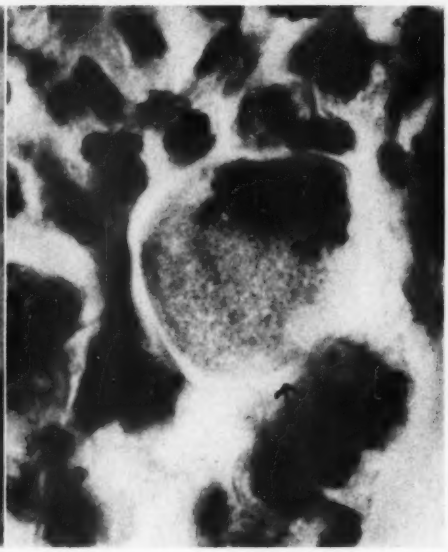
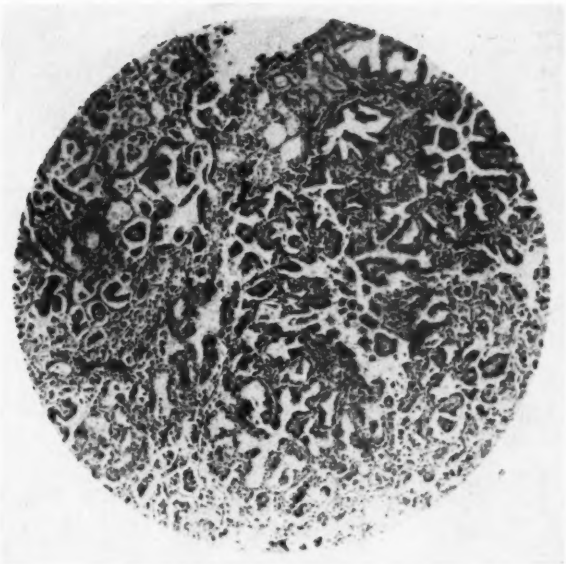


14



15

CHRONIC LEPTOMENINGITIS AND EPENDYMITIS CAUSED BY USTILAGO, PROBABLY U. ZEAE (CORN SMUT)

USTILAGOMYCOSIS, THE SECOND REPORTED INSTANCE OF HUMAN INFECTION *

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It is well known that certain fungi which are saprophytic in their more common or natural habitat are pathogenic for man, and at times produce significant disease. The following saprophytic fungi are proved pathogens for man: *Coccidioides immitis* (coccidioidomycosis) may be found in the air or in the soil; *Candida* (*Monilia*) *albicans* (moniliasis) may be a saprophyte in nature; species of Actinomyces or Nocardia (actinomycosis) can be isolated from the soil; *Zymonema* (*Blastomyces*) *dermatitidis* (North American blastomycosis) is in all probability a saprophyte; *Paracoccidioides brasiliensis* and *P. cerebriformis* (South American blastomycosis or Lutz-Splendore-de Almeida disease) can be found as saprophytes on coffee plants; *Phialophora verrucosa* and other organisms which cause chromomycosis (chromoblastomycosis) can be found growing saprophytically on logs or decaying wood; *Sporotrichum schencki* (*sporotrichosis*) has been found on barberry bushes and other plants as a saprophyte; Aspergillus, Mucor, and other fungi which produce human diseases are air-borne; *Rhinosporidium seeberi* (rhinosporidiosis) in all probability is water-borne. There are, no doubt, other pathogenic fungi producing human disease that have saprophytic existences, the sources of which are unknown.

It has been frequently suggested, but seldom proved, that fungi pathogenic to plants might, under favorable conditions, parasitize man. It is a well known fact that certain mycotic phytopathogens can act as antigens to produce sensitization in man. Cadham,[1] in 1924, had three patients who developed asthma from contact with grain rusts. The chief fungus thought to be responsible for the disease was the wheat rust, *Puccinia graminis*. Hopkins, Benham, and Kesten[2] reported a case of asthma in which the inciting cause was an Alternaria. Several species of Alternaria produce diseases in plants. Among these may be listed *A. mali* (apple leafspot disease), *A. solani* (early blight of potatoes), and *A. panax* (ginseng blight). Other investigators found, as did Brown,[3] that patients were sensitive to numerous fungi that in certain instances were plant pathogens.

* Received for publication, July 23, 1945.

Actual invasion of human tissues by plant pathogenic fungi, however, is rare, in spite of the large number of fungi saprophytic on plants which may affect man. Of particular interest is the case reported by Preininger [4] of a 31-year-old farmer who spent the night in a corn field in a drizzling rain after working in the field under a scorching sun. An examination of the patient revealed that he had a symmetrical arrangement of skin lesions which corresponded to the areas in contact with the wet clothing. These consisted of infiltrated, hyperemic patches on the chest, back, arms, inguinal region, and legs, with scaly plaques in the axillae, on the neck, elbows, and dorsum of the feet. There were scattered red papules on the chest, legs, and buttocks. The hyperkeratotic epidermis of the palms and soles was raised in the form of large sheets of lamellae and revealed an infiltrated corium. A microscopic examination of scrapings from the lesions disclosed spores which were similar to those seen in the black, smutty areas on corn leaves brought from the field in which the patient had slept. The cutaneous disease was thus identified as being caused by the corn smut, *Ustilago zeae* (*U. maydis*).

The above-described case is of interest for two reasons. The first is that it conclusively proves that fungi pathogenic for plants can cause human disease and, secondly, because we have been unable to find in the literature any other case of human infection with Ustilago. It is probably the first proved instance of human infection by *U. zeae*.

Because of the rarity of human disease caused by *U. zeae*, for which the term ustilagomycosis is suggested, it is thought that the following case of chronic leptomeningitis and ependymitis caused by Ustilago is worthy of recording. It is, to the best of our knowledge, the second instance of human infection with this organism and the first in which the infection has involved an internal organ, the brain.

Report of Case

Clinical History. The patient was a white married man, 55 years old, who was admitted to Barnes Hospital on April 29, 1942, and died on May 7, 1942. He complained of a swimming sensation in his head and a staggering gait that had become worse during the 4 months prior to his admission.

The past history revealed that in 1937 he had had an attack of nausea and vomiting for which an operation was performed and a midline epigastric incision was made, but nothing was found. In 1938 he was admitted to a hospital in Louisville, Kentucky, because of staggering, nausea, slight headaches, and attacks of vomiting of 2 years' duration. A cerebellar craniotomy was performed, but no tumor was found and a diagnosis of "chronic cystic arachnoiditis" was made without biopsy. The craniotomy wound did not heal normally and there was continuous drainage from the wound for approximately 4 months. The patient had had defective hearing for a long period. There was no history of meningitis.

Following the cerebellar craniotomy the patient felt well and returned to work as

a farmer which included, among his chores, that of husking corn. He continued to feel well until 4 months before entering Barnes Hospital.

Physical examination revealed a somewhat gruff, almost deaf farmer. At times he seemed unable to understand well, but otherwise he was clear, oriented, cooperative and did not appear to be acutely ill. There was a right lateral nystagmus. Hearing was definitely impaired, more so in the left ear. Since his first illness he had had trouble with his memory and there had been blurring of vision. Adiadokokinesis was present in the left arm. The Romberg test revealed a tendency to fall forward and to the left. The ocular fundi were normal. The reflexes were normal except the abdominal reflexes which were absent. The pulse rate on admission was 56 beats per minute, and the blood pressure was 125/70 mm. Hg. Subsequently the pulse rate increased to 72 beats per minute. On the day before death the pulse varied between 100 and 126, and finally rose to 130 shortly before death. The blood pressure was 125/70 mm. of Hg on admission, reached 138/88, and was 86/74 shortly before death. The temperature fluctuated between 37° and 38° C. and terminally rose to 39° C.

The routine laboratory studies were not remarkable.

On May 5, 1942, a ventriculogram was made, air being injected through a previous perforator opening after 110 cc. of clear fluid were removed from the ventricle. Plates showed the air only in one ventricle. Air was then injected into the left ventricle, following the removal of 60 cc. of fluid. The plates revealed a moderate, symmetrical dilatation of the lateral ventricles, of the third and fourth ventricles, and a prominent aqueduct of Sylvius. Because the ventriculographic studies showed only moderate dilatation of the ventricular system and there were no signs of pressure, it was thought that surgical intervention was not indicated. Thirty-six hours after these studies, the patient developed irregular breathing, became cyanotic and unconscious, and died. Terminally, there were clinical signs of bronchopneumonia that did not respond to chemotherapy and oxygen.

The final clinical diagnoses were hydrocephalus, probably of degenerative type, and bronchopneumonia.

NECROPSY

The external examination of the body disclosed the healed surgical wound in the posterior occipital region, but otherwise nothing remarkable was noted.

The weight of the lungs was moderately increased, the combined weight being 1250 gm. There were scattered fibrous adhesions over the surfaces of both lungs. Irregularly outlined foci of gray, brown and red consolidation, varying from a few mm. to 2 cm. in diameter, were found in all lobes of the lungs. The intervening parenchyma was subcrepitant and gray to pinkish red. A small amount of frothy mucus was present in the trachea and bronchi. A calcified nodule, 2 mm. in diameter, was present in the pulp of the spleen. There were small yellow foci in the intima of the pulmonary, cerebral, and coronary arteries. Similar foci were present beneath the endocardium of the anterior leaflet of the mitral valve. In the wall of the aorta and the splenic arteries there were raised yellow plaques. Except for small deposits of fat beneath the endocardium of the left ventricle, there was nothing remarkable in the heart. There were no gross pathologic changes in the liver, spleen, skin, kidney, or gastrointestinal tract.

Examination of the Brain. The occipital bone showed the trephine openings and the occipital craniotomy. The dura mater was unusually tense and the cerebral convolutions were flattened. A pointed glass tube was inserted into the right lateral ventricle and clear fluid was obtained under pressure. There were fibrous adhesions between the cerebellum and the dura mater. There was a herniation of the cerebellar tonsils into the foramen magnum. The leptomeninges over the cerebral hemispheres and over the base of the brain were slightly thickened and light grayish white. No pathologic change was noted in the basilar arteries.

Following fixation in 3 per cent neutral formaldehyde, the brain was sectioned in a coronal plane, the sections being taken at distances of from 1 to 4 cm. apart. There was moderate symmetrical dilation of the lateral, third, and fourth ventricles. The aqueduct of Sylvius was widely patent, measuring 4 mm. in diameter. The foramina of Luschka and Magendie were obliterated by fibrous adhesions in the subarachnoidal space. There was a faintly visible fine granularity of the ventricular ependyma. There was no gross pathologic change in the brain tissue.

Microscopic Examination

Lung. Several sections taken from the foci of consolidation showed essentially the same pathologic change. The alveoli and bronchi contained polymorphonuclear leukocytes, fibrin, macrophages, and scattered red blood cells. The alveoli in the remaining parenchyma were partially filled with a lightly eosinophilic-staining precipitate which appeared finely granular.

Brain. Sections from the cerebral cortex, cerebellum, and pons (stained with hematoxylin and eosin) showed a chronic inflammatory change in the leptomeninges. Moderate numbers of lymphocytes, plasma cells, and macrophages were present, with a moderate increase in connective tissue. Occasionally a grouping of a multinucleated giant cell and macrophages suggested a tubercle. In the perivascular spaces of Virchow-Robin, adjacent to the pia-glial membrane, there were lymphocytes and plasma cells, in certain instances filling the space.

The section through the medulla including the fourth ventricle disclosed a broad zone of chronic granulation tissue replacing the normal ependymal surface (Fig. 1). In the granulation tissue were large numbers of lymphocytes, plasma cells, large mononuclear macrophages, epithelioid cells, and multinucleated giant cells of the Langhans' type. There were scattered eosinophils and polymorphonuclear leukocytes. The giant cells demonstrated a remarkable variation in size and shape. The peripherally arranged nuclei were usually vesicular and the cytoplasm in most instances was homogeneous, but occasionally contained

fine vacuoles. The chronic inflammatory tissue lining the ventricle contained branching, yeast-like forms of a fungus within many of the giant cells, occasionally in macrophages, and scattered among the inflammatory cells in the granulation tissue. In the sections stained with hematoxylin and eosin the fungi were seen in faint outline, giving the cell a vacuolated appearance, suggestive of phagocytized fat (Fig. 5). In sections stained by the Gram-Weigert method, the fungi were intensely colored and were seen clearly as hyphae or chains of budding or sprouting mycelium. Some of the fungi showed branching (Figs. 2, 3, 13, and 14) and others presented a whorling configuration (Fig. 4). Clear zones surrounded the fungus within the giant cells in practically all instances. These zones were interpreted as the result of a lytic action on the part of the growing fungus.

A post-mortem culture of blood from the heart on blood agar revealed only diphtheroids, regarded as contaminants.

Anatomic Diagnoses

Chronic mycotic leptomeningitis and ependymitis; moderate internal hydrocephalus; healed wound of an occipital craniotomy; cerebellar pressure cone; bronchopneumonia of all lobes of the lungs; lipoidosis of the pulmonary, cerebral, and coronary arteries; arteriosclerosis of the aortic and splenic arteries; and fatty infiltration of the myocardium.

Mycology

The classification of a pathogenic fungus is usually determined by studying the evolution of the organism in artificial mediums and by identifying the various morphologic and physiologic entities which comprise the genus and species. For one trained in mycology, it is usually not difficult to identify, at least generically, most fungi in tissue. An exact identification of the fungus causing the intracranial disease in this case was difficult chiefly because the organism could not be studied on artificial mediums. A chronic infection, especially one due to a fungus, was not suspected at the time of necropsy to account for the slight opacity and thickening of the leptomeninges. Consequently, the entire brain was fixed in formaldehyde, making cultures impossible. Moreover, the appearance of the cells in the tissue, when first examined, gave no clue to their identity. The examination of serial sections of the block of tissue taken from the fourth ventricle, where the organisms were found, revealed that these mycotic structures were apparently morphologic forms known as sprout mycelium. Sprout mycelium is a form of vegetative mycelial growth which develops under certain conditions of nutrition and environment.

A review of the known human mycoses failed to reveal sprout my-

celium in parasitized human tissue of the type observed in this case. The fungi of such granulomatous diseases as blastomycosis, paracoccidioidal granuloma, and histoplasmosis are seen in tissue chiefly as budding cells, either simple or multiple. The organisms causing chromomycosis are seen as simple or multiple cells with septum or cross-wall formation, but no buds, while the characteristic structure of the organism of sporotrichosis is a cigar- or oval-shaped cell. The fungus of coccidioidomycosis or the progressive form of the disease, coccidioidal granuloma, is seen as an endosporulating structure. The fungi causing actinomycosis and maduromycosis when observed in tissue are in the form of branching fine filaments, bacillary cells, or granules composed of filaments and spores. *Candida* (*Monilia*) *albicans* and its related organisms, the cause of moniliasis, a disease which may have a systemic distribution but is usually cutaneous, shows budding, yeast-like cells in tissue. Under certain conditions, *C. albicans* may show filaments or pseudomycelium, but never of the type seen in the case described here. The dermatophytes, including such fungi as produce microsporosis, trichophytosis, epidermophytosis, endodermophytosis or tinea imbricata and favus, present filaments, spores, or chains of cells which may be branching, but are not sprout cells of the type found in this case. Furthermore, the dermatophytes cannot be considered as systemic invaders in the sense that they produce internal lesions of a serious nature, particularly of the brain. Likewise, there is a marked difference in appearance of the hyphae and spores of Aspergillus, Mucor, Penicillium, and other genera of the so-called "weeds of mycology" which may produce systemic disease.

A clue to the probable identity of the fungus was found only after studying the organism in all its forms in the serial sections. This clue was a germinating spore which was engulfed by a giant cell (Fig. 6). The outer wall of the spore appeared thick and had surface markings which consisted of small excrescences or spines. The germinating portion of the structure appeared to be protruding through a split wall, was thin-walled, nonstaining or hyaline in character, and blunt at the growing tip. A combination of the sprout mycelium plus the spiny, germinating cell suggested the characteristics of a smut organism. This supposition was further strengthened by the finding of a spore in a clear space within a macrophage which was characteristic of an immature or young smut spore with the thick, dark wall and the single nucleus (Fig. 7). Further search in other slides from the fourth ventricle and also in the choroid plexus of the fourth ventricle was rewarded by the finding of an elongated, irregularly elliptical, spiny or echinulate spore (Fig. 8), a chain of echinulate spores (Fig. 10), and

masses of spiny spores and germinating forms in the choroid plexus (Figs. 11 and 12). For the most part, the spiny spores were globose (spherical) with the exception of a few which were subglobose to ellipsoid or irregular. The mature globose spores that were observed measured approximately 7 to 10 μ in diameter, whereas the elongated spores were approximately 11 μ in the long axis.

The Ustilaginales or smuts include several hundred species which parasitize higher plants.[5] Of this large number, many can be eliminated in an attempt to classify the fungus in the case presented here on the basis of spore size and spore surface markings or absence of markings. The cereal smuts are the more common forms encountered on farms. The work of Stakman [6] has been of great help in eliminating certain cereal smuts on the basis of spores and spore germination.

Ustilago hordei, the covered smut of barley, can be eliminated since the mature spores are smooth and do not have spines. *Tilletia foetens,* the stinking smut of wheat, likewise has smooth-walled spores. In *Ustilago tritici,* the loose smut of wheat, the spores are lighter on one side than on the other and the spines are usually seen on the lighter side, sometimes along the edge on optical section and sometimes covering only half the spore. The spore wall is rarely split by the promycelium and usually the promycelium is constricted at the base, precisely where it emerges from the spore. Since the spores observed in our sections showed spines over the entire wall, splitting of the spore wall and no constriction of the germination at the base, it is safe to eliminate this organism. *U. nuda,* the cause of loose smut of barley, has spores which resemble those of *U. tritici.* The spores of this organism appear hollowed out in the center, giving them a concave appearance. This feature was not observed in the spores seen by us. The spores of *U. avenae,* the smut of oats, resemble those of *U. tritici* and *U. nuda.* The spores of *U. zeae,* also known as *U. maydis,* the cause of corn smut, have characteristics similar to those of the organism noted in the sections from our case.

In plants, *U. zeae* produces what is known as a smut tumor. The tumor is covered with a thin membrane which encloses the mass of powdery spores in addition to the parenchymal cells and fibrovascular bundles of the host. When the membrane ruptures, the mature spores are set free and scattered by the wind or drop down to contaminate the soil in the vicinity. The mature spores measure approximately 7 to 12 μ in diameter, are usually spherical, but may be ellipsoid or irregular in shape and vary less from the normal than do the spores of *U. tritici* and *U. nuda.* The spores are brown, and are not lighter on one side than on the other, but the individual spores may vary some-

what in density, some being darker around the edges, especially on optical section, appearing dark brown to black. The outer wall or *epispore* is covered with prominent spines or warty excrescences which show distinctly on all sides. Under satisfactory conditions of temperature and moisture the spores will germinate, but when unfavorable they will remain dormant, retaining their viability for several years or until such time as growth conditions are again favorable.

The relation of temperature to germination was studied by Jones [7] who found the optimum temperature for corn smut to be between 26 and 34° C., the maximum between 36 and 38° C., and the minimum 8° C. The optimum is higher than for most smuts and helps make clear two important points. The first is that this tolerance to high temperature explains why corn smut is more severe in the warmer regions where corn is grown, and the second is that that may be the reason why the fungus is able to produce lesions in the human body.

When the mature spore germinates, it forms a special structure known as the *promycelium* which is made up of four somewhat elongated cells. From these promycelial cells there develop, laterally and terminally, secondary structures termed *sporidia* which are fusiform and vary in size. Under continued favorable conditions, the promycelium will branch and produce a large number of sporidia. Some of the sporidia will become elongate to form so-called infection threads, while others will bud as do yeasts to produce secondary sporidia or sprout cells. When the budding cells reach the air or when there is a changed oxygen tension, the sprout cells form branches or chains of cells, many irregular in shape and size. These break off and are scattered by the wind to germinate and produce localized tumors when they reach young corn plants. The time for the development of mature spore sacs, depending upon the environment, varies from approximately 1 to 3 weeks. More information can be had by reading one of the standard texts on plant diseases such as that of Heald.[8]

It is apparent from the foregoing that the various stages of the fungus that we have observed in human tissue strongly suggest Ustilago, probably *U. zeae,* as the causative agent of the infection. In summary, these stages consist of: the sprout mycelium which grows under altered conditions of nutrition and oxygen tension; the young or immature spore which shows the characteristic thick wall and nuclear structure; and finally the mature, germinating spores with the varied shapes and sizes, and spines or warty excrescences. Unfortunately, conclusive proof of the identity of the pathogen, namely, its cultivation on artificial mediums, was not possible since the brain was fixed in formaldehyde before it was known that the disease was caused by a

microorganism. However, in spite of the lack of cultural studies we feel justified in considering this case as an example of systemic disease caused by a smut organism that was in all probability that of corn, *U. zeae.*

Discussion

It is difficult to hazard a reasonable guess as to the portal of entry of the fungus. A review of the case history, however, suggests at least two possibilities. The first possibility is that of contamination through the drainage tract following cerebellar exploration, and the second is by way of the gastrointestinal tract. In favor of the first is that shortly after the operation the patient went to work on the farm, and included among his chores was that of husking corn. Although on first thought this appears as a plausible explanation, it does not explain the genesis of the patient's intracranial disease prior to the operation upon which a diagnosis of chronic cystic arachnoiditis was made. Moreover, the draining wound following craniotomy would suggest that the disease was present before the operation, a reasonable explanation for the failure of the wound to heal normally. In favor of the second possibility is that prior to the cerebellar craniotomy the patient had had an attack of nausea and vomiting of such severity as to lead to a laparotomy. It would seem, therefore, that conclusive evidence is lacking to substantiate either of these possibilities, but that the gastrointestinal tract appears to be the more likely portal.

It has been known for a long time that corn smut contains an active principle, probably an alkaloid, which exerts an action similar to that of ergot. The alkaloid, when ingested by cattle, affects the nervous system to produce what is known as "staggers" (grass staggers or stomach staggers).[9] Highly nitrogenous feeds have also been blamed for causing this disease. In this respect it is worth while to mention that analyses of corn smut have shown that it has a high carbohydrate content and more protein than is found in corn, oats, or clover hay. The symptoms of staggers vary, but generally they indicate involvement of the nervous system. The first symptoms are somnolence and hypoactivity with subsequent general signs of frenzy. The animal is constipated and the output of urine is small. The urine is darker than usual. There may be trembling and spasms of muscles in different parts of the body. In the dull stage, respirations are depressed and each expiration may be accompanied by a sound like snoring. The pulse rate is low, but the volume is good. When aroused suddenly from the drowsy state, the animal appears startled and stares wildly. When moving about it may stagger, with the hind quarters swaying from side to side.

In the advanced stage, when delirium sets in, a cow is said to be mad, having such symptoms as bellowing, stamping of feet, running about wildly, grating of teeth, and frothing at the mouth. There is muscle twitching and jerking and the body may become covered with perspiration. These symptoms are frequently accompanied by convulsions followed by a prolonged period of coma. When consciousness is regained, the animal may get up on its feet, quietly eat some food, or blindly stagger about. Not all of these symptoms, however, are always present in the same animal. When the symptoms of drowsiness are present it is called "sleepy staggers," and when the symptoms are those of frenzy it is called "mad staggers." Frequently the animal will be paralyzed and remain so until death. Post-mortem examination reveals congestion of the brain, meninges, and lungs.

Ergotism is a rare disease in man and is uncommon in America. Ergot-like symptoms caused by *U. zeae* (*U. maydis*) and termed ustilaginism by Mayerhofer [10] likewise are rare. Von Storch,[11] in 1938, listed the symptoms and signs of the *gangrenous* and *convulsive* or *neurogenic* types of ergotism in man following the use of ergotamine tartrate in the treatment of migraine headache. As described, the two types when combined bear a striking similarity in many respects to the combined symptoms of ustilaginism described by Mayerhofer [12] in children.

According to von Storch,[11] the symptoms and signs of 42 cases of ergotism showed with the gangrenous type lassitude, dullness, vague lumbar pains, cramps in the calves of the legs, and dull burning pain in the extremities followed by waves of heat or cold leading to numbness. There were also noted vomiting, and swelling of the feet with the skin of the extremities becoming cold and reddish violet, and developing vesicles which preceded the blackening of the gangrene which was usually dry. Jaundice was commonly observed. The convulsive or neurogenic type was characterized by fatigue, heaviness of head and limbs, giddiness, insomnia, excitement leading to delirium and mania, with impaired sight or hearing and formication. There were painful spasms of the face, throat, and diaphragm; tonus, clonus, myoclonus, contractures, myopia, myosis, vomiting, diarrhea and amenorrhea. Pseudotabetic, hemiplegic, or paraplegic symptoms have been described.

The symptoms observed in a number of cases of ustilaginism by Mayerhofer [10, 12] are remarkably similar to the symptoms of ergotism described by von Storch.[11] Mayerhofer described intense itching of the body and the extremities; itching, redness, and swelling of the nasal and buccal mucous membranes; marked scaling of thick, dry

crusts on the soles and palms; either intense sweating or none, with usually an elevated temperature in the beginning; muscle weakness and rheumatic types of pains; redness, swelling, and heat in the distal part of the extremities followed by pigmentation of the affected parts; gastrointestinal disturbances following the ingestion of corn flour containing corn smut or ergot; diminishing desire to eat and strong feeling of thirst; gastro-enteritis and colic; gangrene of the extremities, usually dry; latent or manifest tendency toward spasms, eclampsia-like symptoms, cramps, contractures, catatonia, delirium, mania; increased blood pressure with tachycardia preceded in the beginning by bradycardia; exacerbation of symptoms by sunlight; rapid cure if diagnosed early; severe disease in the late stages, with possible death.

It is easily seen from the foregoing that ergotism and ustilaginism in man and animals have enough symptoms and signs in common so that they may be regarded as similar toxic phenomena. In addition to the clinical aspects, post-mortem findings in cases of ergotism in man usually reveal hyperemia, edema, and hemorrhage in the gastrointestinal tract, lungs, and brain. These observations, although not diagnostic of the disease, are generally those seen in animals dying from eating corn smut.

It is interesting to note that there were observed in the patient studied here symptoms similar in many respects to those described for "staggers" in animals. The patient's chief complaint was staggering; he had had gastrointestinal disturbances of a proportion to necessitate an abdominal operation. Other complaints suggesting ergotism included nausea, vomiting, and some neurologic signs. The general clinical picture, however, was not that observed in the most advanced cases of ergotism or ustilaginism. Gangrene of the extremities, marked scaling of the skin, redness and swelling of the mucous membranes, and the more advanced neurologic signs were not observed in this patient. It should be noted, however, that the severest symptoms and the most advanced lesions were not observed in all cases of ergotism and ustilaginism.

The pathologic changes produced by the ingestion of the toxic principle of Ustilago in animals are most marked in the brain (leptomeningitis) with an accompanying edema and congestion of the lungs. In rats, Tichomirov and Bogdanovic [13] observed fatty degeneration of the myocardium with some fragmentation of the fibers, degenerative changes in the kidneys with foci of calcification, and thickening of the intimal layer of blood vessels with hyalinization of the cells. In human ergotism the changes noted are hyperemia, edema and hemorrhage in the brain, lungs, and gastrointestinal tract.

The pathologic changes observed in the case reported here are compatible with the aforementioned changes observed in spontaneous and experimental Ustilago poisoning in animals. However, it should be emphasized that the observed pathologic changes described for Ustilago intoxication are not in any way to be regarded as in themselves sufficiently characteristic to be diagnostic of this particular intoxication. In the patient studied here there were observed pathologic changes in the leptomeninges and the ependyma which were the site of an inflammatory disease produced by the microorganism. At best, congestion and edema of the brain are difficult to evaluate properly when the examiner is looking for them. These changes were not looked for specifically at the necropsy.

It is interesting to note that there was a deposition of lipoid material in the intima of several arteries and beneath the endocardium of the left ventricle. Comparable changes have been described by Tichomirov and Bogdanovic[13] for their rats with experimentally induced ustilaginism. However, it is impossible to attach great significance to these pathologic changes since they are so frequently seen in routine autopsies.

Summary

A case of chronic leptomeningitis and ependymitis caused by a species of the genus Ustilago, *U. zeae*, the corn smut fungus, is described. No other focus of infection was found in the body and it was not possible to determine with certainty the portal of entry and how the leptomeninges and ependyma became infected. The microorganism was identified by the finding of characteristic germinating spores in the fourth ventricle. Histologically, the fungus produced a granulomatous reaction in the leptomeninges and the ependyma with giant cells of the Langhans' type within which the fungus frequently produced sprout mycelium. Clinically, the patient manifested some of the signs and symptoms that have been described in man and animals affected with ergotism and ustilaginism.

This case is believed to be the first instance of systemic infection produced by Ustilago to be reported, and the second proved case of human infection with an organism of this genus. The term, ustilagomycosis, is suggested for the granulomatous tissue change produced by fungi of the genus Ustilago.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 148

All photomicrographs were made from sections of the posterior portion of the fourth ventricle.

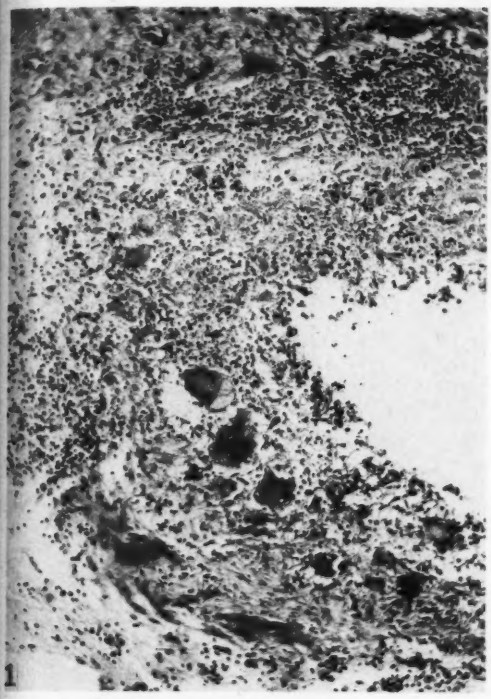
FIG. 1. Granulomatous reaction in tissue, showing giant cells and cellular infiltrate. Gram-Weigert stain. × 95.

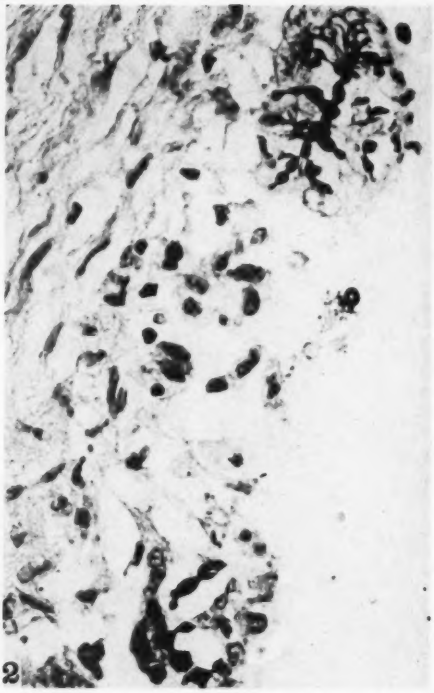
FIG. 2. Giant cells in meningeal tissue showing sprout mycelium. Gram-Weigert stain. × 480.

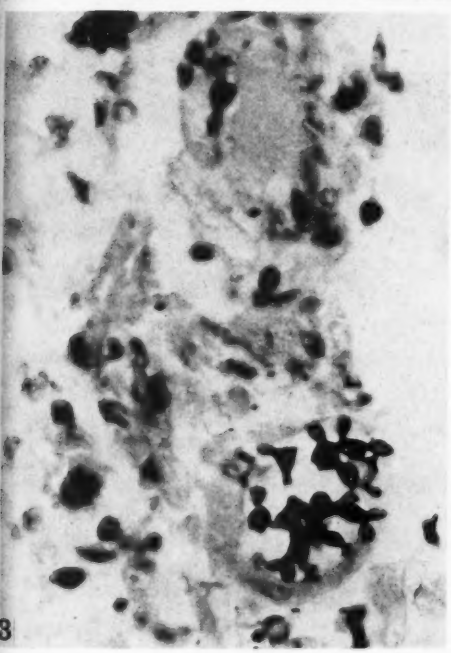
FIG. 3. Giant cells engulfing organisms. Gram-Weigert stain. × 650.

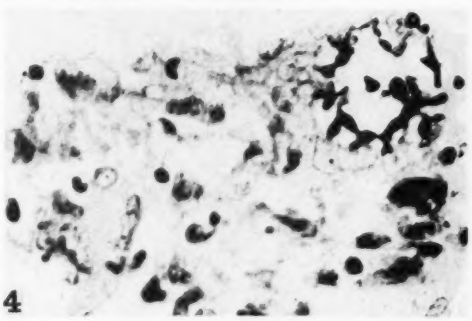
FIG. 4. Giant cells engulfing organisms. Gram-Weigert stain. × 495.

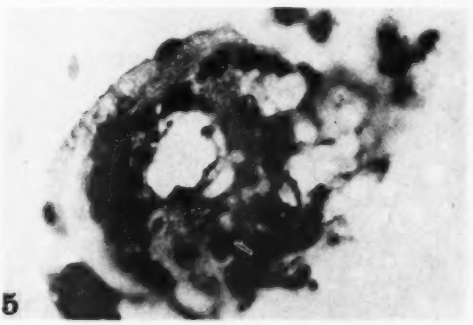
FIG. 5. Giant cell showing clear zones within which are faintly stained fungus cells. Hematoxylin and eosin stain. × 530.











Moore, Russell, and Sachs Ustilagomycosis

Plate 149

All photomicrographs were made from sections of the posterior portion of the fourth ventricle.

Fig. 6. Germinating, mature spore of Ustilago in giant cell. Of note are the thick, spiny epispore and faint, blunt beginning of the promycelium. Gram-Weigert stain. × 1510.

Fig. 7. Young, immature spore in macrophage. Of note are the thick wall and clear zone around the fungus cell. Gram-Weigert stain. × 1510.

Fig. 8. Elongated, spiny or echinulate spore. Gram-Weigert stain. × 1510.

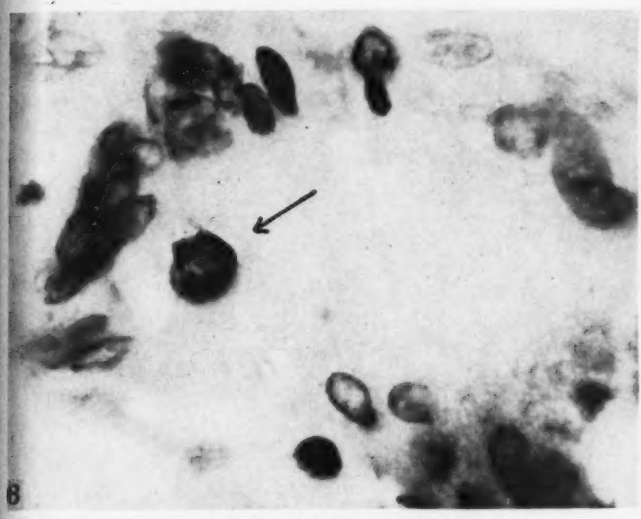
Fig. 9. Germinating cell showing development of promycelium. Gram-Weigert stain. × 1510.

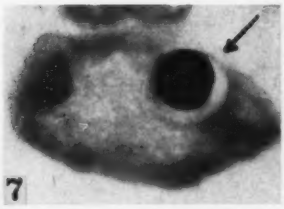
Fig. 10. Chain of echinulate spores. Gram-Weigert stain. × 1510.

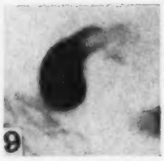
Figs. 11 and 12. Groups of mature germinating cells in the choroid plexus. Gram-Weigert stain. × 1510.

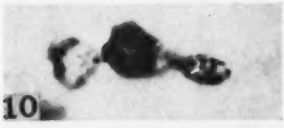
Fig. 13. Sprout mycelium. Gram-Weigert stain. × 1290.

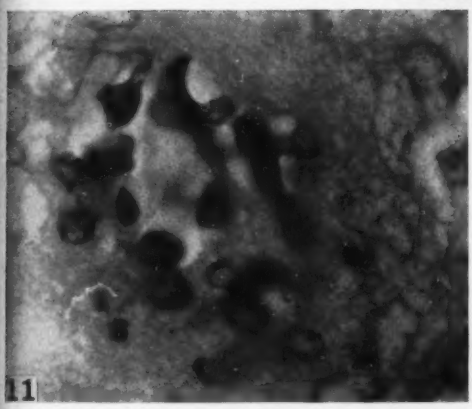
Fig. 14. Sprout mycelium, showing budding. Gram-Weigert stain. × 1290.

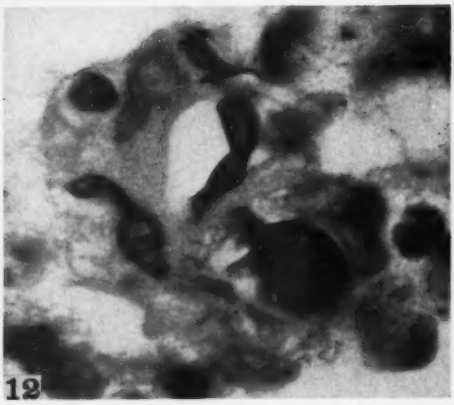


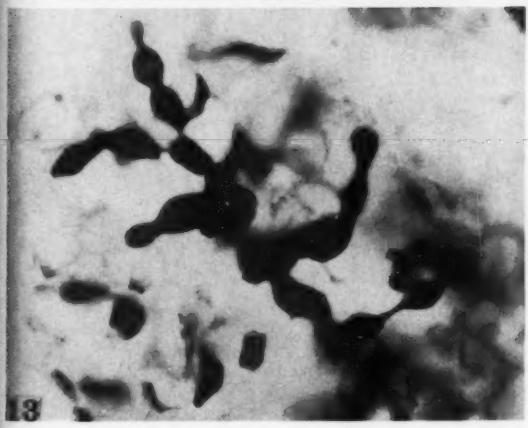


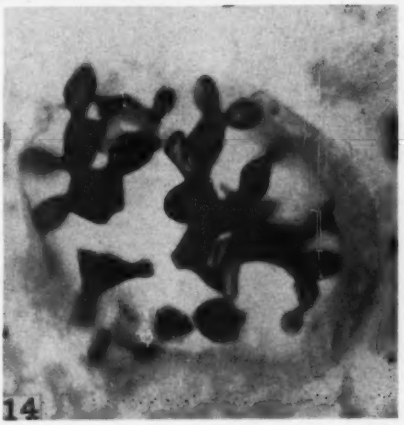












SYSTEMIC INFANTILE TOXOPLASMOSIS *

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The number of cases of toxoplasmosis, reported since human infection by this protozoon became unquestionably established, indicates that it is a disease of increasing clinical importance. The world-wide distribution of Toxoplasma in animals and the widespread geographic areas from which human cases have been reported show that its epidemiology is potentially of great significance. The variable clinical and subclinical manifestations that result from toxoplasmic infestation and the unsolved problems regarding its transmissions are factors which make the recording of any additional information desirable. We have recently studied a newborn infant who died of a fulminating and widely disseminated toxoplasmic infection which we will describe in detail. This is the first instance of the disease in South Carolina, and, so far as we have been able to determine, is the first case to be reported from the southeastern states. Only 21 cases proved by necropsy are recorded in the literature. Of these, 15 cases, including the one reported here, occurred in infants, 2 in children, and 4 in adults. In 12 of these cases organisms were found in tissues outside the central nervous system (Table 1).

Report of Case

A boy, weighing 5 lb. 11½ oz., was born to healthy white parents on December 26, 1943. The parents had been married for 18 months and it was the woman's first pregnancy. Labor and delivery were uneventful. The infant was slightly cyanotic at birth, particularly about the face. The cyanosis became more intense and generalized. Edema developed which pitted on legs and abdomen and was brawny and indurated over thighs, buttocks, back, upper arms, and face. Respirations were normal and the pulse regular. There were no heart murmurs. The liver and spleen were palpable, the former being 3 fingersbreadth below the costal margin. The cyanosis persisted and the abdomen became distended. The infant had no bowel movements and on rectal irrigation mucous casts and a little meconium were obtained. The edema was gradually absorbed, but the baby became steadily weaker. Five days after birth he developed distinct signs of cerebral irritation with nystagmus and recurring attacks in which the eyes rolled upward, accompanied by fixation of muscles of the face and irregular movements of the arms. Convulsive movements became nearly continuous shortly before death on December 31, 1943.

The parents were natives of Hendersonville, N. C. The father was 23 and the mother 21 years of age. They had lived in a trailer camp in the congested area adjacent to the Charleston Navy Yard for 11 months immediately prior to the baby's birth. The only animal with which they had come in contact was a dog. This pet was described as healthy. The parents had always been in good health, having had no serious or unusual illnesses. The mother was in an automobile accident when 5 months' pregnant, following which she experienced a few transient abdominal pains. Kline exclusion test of her blood was negative.

* Received for publication, July 23, 1945.

REPORT OF NECROPSY

The body was that of a well developed and apparently full-term male infant whose sclerae and skin were lemon yellow. There was some puffiness of the face and lids and the skin appeared thickened, although there was no pitting edema.

There were 25 cc. of orange-colored fluid in the peritoneal cavity.

The right lung weighed 33 gm. and the left lung, 35 gm. Both were subcrepitant and reddish purple, with scattered areas of rubbery consistency. The right lung was intensely congested and there were small hemorrhages beneath the visceral pleura. Hemorrhages were present also beneath practically the entire parietal pleura on the right.

The heart weighed 19 gm. The myocardium had a mottled reddish yellow color. Beneath the epicardium, particularly in the atrioventricular groove, were multiple hemorrhagic foci.

The deep-chocolate-colored liver weighed 137 gm.

The spleen weighed 27 gm. and its capsule was dull and coated with strands of greenish yellow material. The pulp was firm and deep purple. A nodule of accessory splenic tissue, 6 mm. in diameter, was present.

The adrenals were of normal size and shape. On section there was a faint rim of yellowish tissue about the soft brownish gray centers.

The kidneys were of normal appearance.

The sigmoid colon was moderately dilated and contained a large amount of sticky, gummy meconium.

The brain weighed 334 gm. The meninges were slightly cloudy, particularly along the sulci, and an increased amount of brown-tinged fluid was present in the subarachnoid space. There was an area of hemorrhage beneath the pia arachnoid over the left parietal lobe adjacent to the median longitudinal fissure. Multiple sections revealed numerous irregular, brownish red and yellow areas scattered throughout the cerebral hemispheres, pons, medulla, and cerebellum. These discolored foci were often slightly depressed and moth-eaten in appearance. They were most conspicuous in the subcortical white matter, dentate nuclei, and basal ganglia, particularly the thalami. No gritty particles or other evidence of calcification were found. Many of the vessels were markedly engorged, and some had perivascular hemorrhages, one in the parietal region measuring 4 mm. in diameter.

Histologic Findings

Heart. There was widespread inflammatory involvement of the entire heart wall with multiple foci of necrosis (Fig. 1). The myocardium and endocardium were most heavily involved, the inner portion of the myocardium slightly more than the remainder. The reacting cells

consisted chiefly of lymphocytes and histiocytes with moderate numbers of polynuclear leukocytes, most of which were eosinophils. The inflammatory cell collections were variable in size and often ill defined, but they tended to be focal. The infiltration often involved the supporting fibrous framework and the walls of arteries and veins. The areas of necrosis were chiefly myocardial, however. Inflammatory cell collections in the subendocardial connective tissues were often associated with roughening and even erosion of the overlying endothelium. Some groups of immature blood cells were present. Accumulations of toxoplasmata were easily found within the muscle cells (Fig. 2). In longitudinal section these aggregates were ovoid or spindle-shaped and in cross section were round. Smaller groups of organisms were also present in the myocardial fibers and were often surrounded by a clear space (Fig. 3). Individual organisms were found in and about some of the inflammatory foci and in areas of early necrosis. The circumscribed aggregates of parasites were invariably free from accompanying cellular reaction. Toxoplasmata were also found in the endothelial cells of small arteries, the cells being so swollen and filled with organisms in a few instances as nearly to occlude the lumen. The individual organisms were rounded or ovoid and contained a chromatin mass which was usually situated eccentrically or at the larger end (Fig. 3). They measured 3 to 5 by 2 to 3 μ in diameter, individual organisms generally being larger than those within the pseudocytes.

Lung. Many of the pulmonary alveoli were collapsed. Their walls were thickened and infiltrated by mononuclear cells and occasional polynuclear leukocytes. Within the alveoli were clumps of macrophages with foamy or granular cytoplasm and groups of swollen, cast-off, alveolar lining cells. Networks of fibrin, occasionally mixed with leukocytes, were also present. There was intense congestion throughout, with areas of hemorrhage into alveoli, subpleural connective tissue, and fibrous septae. Some alveoli contained a few strands of vernix caseosa and degenerated epithelial cells. Scattered groups of immature blood cells, chiefly of the erythrocytic series, were found. Toxoplasmata were found in the lining cells of the alveoli (Fig. 4) and in the endothelium and walls of blood vessels. Some alveolar cells contained as many as fifty parasites, whereas five were the most ever noted in a single endothelial cell.

Liver. Moderate cloudy swelling of hepatic cells was present, with small fat vacuoles scattered diffusely through the cytoplasm of many. The cells showed bile staining and the canaliculi were stuffed with bile. The lumina of nearly all ducts were open, but an occasional small duct was filled with bile. No definite necrosis was found. Numerous hemato-

poietic foci were present, normoblasts being particularly conspicuous and immature cells of erythrocytic type generally predominating over those of the leukocytic series. These blood-forming cells were also abundant in the fibrous stroma of the portal areas and about the larger portal veins. Many of the cells were eosinophilic myelocytes, particularly in the latter locations. Toxoplasmata were found in the Kupffer cells and in the endothelium of small vessels. There were no lesions for which Toxoplasma definitely could be held accountable.

Spleen. The spleen showed marked increase in the cellularity of the pulp due to the number of hematopoietic cells. Deposits of fibrin were present in the red and white pulp and on the capsular surface. Toxoplasmata were occasionally found in the endothelium of blood vessels, but there were no granulomas or areas of necrosis.

Kidney. The cytoplasm of the swollen epithelial cells of the convoluted renal tubules was granular and vacuolated. The tubular lumina contained granular orange-brown material and occasionally in the epithelium there were fine yellowish granules. The glomeruli appeared normal. Two adjacent veins in the pelvic area showed early thrombosis. The interstitial tissues contained a few foci of hematopoiesis. Toxoplasmata were found in the endothelium of arterioles, but they were sparse, and no lesions for which they definitely could be held responsible were found.

Adrenal. The inner two-thirds of the adrenal cortex showed profound degeneration with marked cellular swelling and vacuolization of the cytoplasm. Rounded areas of coagulation necrosis were present throughout this zone as well as less numerous and smaller areas of leukocytic and mononuclear cellular infiltration, a few of which resembled the granulomas in the brain. Accumulations of toxoplasmata were easily found and individual organisms, often degenerating, were also present, but these were identified with greater difficulty.

Stomach. Small focal areas of necrosis were present in the gastric musculature with infiltration of lymphocytes, histiocytes, and eosinophils. Similar reacting cells were scattered irregularly throughout the wall, but were most heavily concentrated about blood vessels. Toxoplasmata were found in groups within the smooth muscle cells and singly in and about the inflammatory foci.

Intestine. The intestine showed edema of the submucosa and subserosa with infiltration of eosinophils and mononuclear cells. In one section the inflammatory reaction was particularly intense and neutrophils were the predominant cells. Toxoplasmata were found in the epithelium of the mucosa, but no organisms could be identified in the muscle coats or in the most heavily inflamed portion.

Pancreas. Edema of the connective tissue framework was found in the pancreas with diffuse infiltration of eosinophils, lymphocytes, and histocytes, and an active vasculitis. Toxoplasmata were found in the vascular endothelium and acinar epithelium.

Diaphragm. Perivascular infiltration of mononuclear cells was present in the diaphragm, with a few small areas of early necrosis in the muscle, some fibers of which contained accumulations of toxoplasmata.

Bone. In sections of thoracic vertebrae the cortical bone and trabeculae were of normal appearance. The medullary tissue appeared moderately hyperplastic, many of the cells being erythropoietic. An occasional protozoan body was identified, a few in the sinusoids and one in an endothelial cell. The free organisms were fusiform, pyriform, or crescentic.

Lymph Nodes. The mesenteric lymph nodes were surrounded by loose fibro-fatty tissue. They showed little definite follicle formation, and the sinusoids were prominent. In addition to the lymphocytic series, immature cells of the granulocytic series, especially myelocytes, were present. Mitotic figures were moderately numerous. Pyriform and ovoid protozoa were found in lymphatic sinusoids, in the swollen endothelial lining cells, and a few were related to blood vessels in the surrounding fibro-fatty stroma.

Thymus. Hassell's corpuscles were the site of cellular fragmentation and hyalinization. Eosinophilic myelocytes were present in the medullary tissue. The capillaries were engorged and a single toxoplasma was noted in a capillary endothelial cell.

Brain. Numerous small granulomas were scattered throughout the brain, including medulla and cervical cord (Fig. 5). These were composed of collections of epithelioid cells that were often fused into groups in which the cell boundaries were indistinct. The granulomas were closely related to capillaries in nearly every instance, the epithelioid cells apparently being derived from the endothelium of these vessels. Mixed with the epithelioid cells were varying numbers of lymphocytes, polynuclear leukocytes, and eosinophils. Definite necrosis was not a conspicuous feature, but occasionally the reacting cells were arranged about a necrotic center so as to resemble a tubercle. In addition to the granulomas there were areas of edema and degeneration containing small numbers of lymphocytes, large mononuclear cells, and occasional polymorphonuclear leukocytes. In and about such areas the vessels were markedly engorged and there were occasional perivascular hemorrhages. A few vessels contained early thrombi. The meninges were edematous and infiltrated by large numbers of macrophages and large and small lymphocytes. In some places extravasa-

TABLE I

Cases of Toxoplasmosis Authenticated by Necropsy

Author	Location	Sex	Age at onset	Age at death	Clinical features	Tissues involved
1. Janku [18, 19] (Levaditi suggested Toxoplasma)	Prague, Czechoslovakia	M	Birth(?) 3 mos.(?)	11–16 mos.(?)	Hydrocephalus, blindness, convulsions, vomiting, chorioretinitis	Eye; no others examined
2. Richter [5] (Toxoplasma discovered by Wolf and Cowen)	Chicago, Illinois	F	6 wks.	7 wks.	Convulsions, fever, "cold," opisthotonus	Brain, spinal cord
3. de Lange [6, 20] (Toxoplasma found by Wolf and Cowen)	Amsterdam, Holland	F	Birth(?)	4 mos.	Hydrocephalus, labile temperature, tremors of arm, vomiting	Brain
4. Wolf and Cowen [21] (Case 1)	New York City	F	2 days	29 yrs.	Convulsions, labile temperature, slight hydrocephalus, vomiting, diarrhea, respiratory disturbances, chorioretinitis	Brain, spinal cord, eye
5. Wolf, Cowen, and Paige [4] (Case 2)	New York City	M	3 days	31 days	Convulsions, vomiting, signs of cervical cord lesions with subarachnoid block, labile temperature, respiratory disturbances, chorioretinitis; enophthalmos	Brain, spinal cord, eye
6. Paige, Cowen, and Wolf [22] (Case 3)	New York City	F	Birth	9 wks.	Hydrocephalus, twitching of lower extremities, labile temperature, convulsions, membranous masses in vitreous, microphthalmos and enophthalmos	Brain, spinal cord, eye
7. Steiner and Kaump [10] (Case referred by Dr. Sailer)	Cincinnati, Ohio	M	Birth(?)	3 days	Hydrocephalus	Brain
8. Zuelzer [11]	Detroit, Michigan	M	Birth(?) 3 days(?)	1 mo.	Listlessness, icterus, cyanosis, rash, labile temperature, labored respirations	Brain, spinal cord, eye

Author	Location	Sex	Age at onset	Age at death	Clinical features	Tissues involved
9. Steiner and Kaump [10]	Detroit, Michigan	M	Birth(?) 1 day(?)	3 days	Petechiae, icterus (erythroblastosis fetalis); fever, cyanosis, twitching of eyes and extremities terminally	Brain; toxoplasmic cysts in adrenal without lesions
10. Torres [9, 19, 23]	Rio de Janeiro Brazil	F	Birth	2 days	Convulsions	Brain, spinal cord, myocardium, skeletal muscle, subcutaneous tissue
11. Hertig [7, 15] (Pinkerton and Weinman identified organism as Toxoplasma; reported by author as sarcocystis)	Boston, Massachusetts	F	?	25 days	2 months premature; fever, diarrhea	Brain, lung, myocardium, adrenal; very little inflammatory reaction about parasites; died of bacterial infection
12. Paige, Cowen, and Wolf [22] (Case 4)	New York City	M Negro	?	Stillborn	Fetal hydrocephalus, microphthalmos and enophthalmos, unilateral	Brain, spinal cord, eye, myocardium, striated muscle, adrenal
13. Paige, Cowen, and Wolf [22] (Case 5)	New York City	F		3½ days	Respiratory difficulty, edema, cyanosis, mild fever	Brain, spinal cord, lungs, myocardium, adrenals, and ovaries; eyes not examined; toxoplasmata, without lesions, found in thyroid, striated muscle and adipose tissue
14. Zuelzer [11]	Detroit, Michigan	M	3 days(?)	11 days	Apathy, drowsiness, cyanosis, convulsions, opisthotonos	Brain, spinal cord, myocardium, lungs, adrenals, kidneys, testicles, striated muscle

TABLE I (Continued)

Cases of Toxoplasmosis Authenticated by Necropsy

Author	Location	Sex	Age at onset	Age at death	Clinical features	Tissues involved
15. Pratt-Thomas and Cannon	Charleston, South Carolina	M	Birth(?)	5 days	Cyanosis, edema, convulsions	Brain, spinal cord, myocardium, lungs, adrenals, stomach, striated muscle and pancreas; parasites without lesions found in liver, bone marrow, spleen, kidneys, lymph node, thymus, and intestine
16. Sabin[13]	Cincinnati, Ohio	M	6 yrs.	1 mo. later	Headache, convulsions, vomiting, weakness of extremities, palpable spleen, fever in latter part of illness	Brain
17. Pinkerton and Henderson[14]	St. Louis, Missouri	M	50 yrs.	8–10 days after onset	Fever, maculopapular rash, diarrhea, pneumonia, oliguria, coma	Lungs, heart and spleen; lesions in skin, but no parasites; brain not examined
18. Pinkerton and Henderson[14]	St. Louis, Missouri	F	43 yrs.	28 days after onset	Weakness, malaise, fever, maculopapular skin rash, chill, headache, pneumonia	Heart, lungs, liver, spleen and brain
19. Pinkerton and Weinman[15]	Lima, Peru	M	22 yrs.	12 days after onset	Weakness, pallor, fever; complicated by *Bartonella bacilliformis* infection that was apparently subsiding	Brain, heart, lungs, liver, spleen, kidneys, lymph nodes, adrenals, skin, bone marrow
20. Guimarães[16]	Brazil	M Negro	18 yrs.	37 days after onset	Paralysis of lower extremities, nuchal rigidity, dysphasia, fever	Brain, spinal cord, pericardium, kidneys
21. Tomlinson[12]	Canal Zone	F Negress	?	10 yrs. 8 mos.	Died of sickle cell anemia	Toxoplasmic pseudocysts in brain and heart; no inflammatory response

tions of erythrocytes were noted also. The vascular channels in the choroid plexus were intensely engorged, and the stroma of the tufts showed variable degrees of infiltration by large mononuclear cells and lymphocytes. Toxoplasmic pseudo-cysts were easily found (Fig. 6). They were never situated in a granuloma, area of degeneration, or inflammatory infiltrate, although some were fairly close to granulomas. Individual organisms were present in and about the granulomas as well as in the epithelium of the choroid plexus. No calcification was present.

Discussion

Since the genus Toxoplasma was first described in 1908, reports of disease produced by it in animals and man have been rather numerous. Wenyon [1] analyzed several debatable cases reported in human beings and concluded that none of them were due to Toxoplasma. He also reviewed much of the literature concerning its occurrence in various forms of animal life in virtually all parts of the world. Olafson and Monlux [2] have recently implicated Toxoplasma as the cause of fatal disease in dogs and also have described cases in cats and sheep, thus suggesting a possible source of human infection. Perrin, Brigham, and Pickens [3] have demonstrated toxoplasmic infestation in 8.7 per cent of a group of wild rats studied in the southeastern part of the United States.

Accepted human cases of toxoplasmosis are not of equally wide geographic distribution, for reference to Table 1 shows that 15 cases are from this country. The first case proved by animal inoculation was reported by Wolf, Cowen, and Paige [4] in 1939, following which a review of cases and study of literature by them and others indicated a similar etiologic agent in the cases of Richter,[5] de Lange,[6,20] and Hertig.[7] In addition, they agreed with Levaditi's [8,19] acceptance of Toxoplasma as the causative factor in the cases of Janku [9,18] and Torres.[9,23] Steiner and Kaump [10] reported a case of their own and made reference to an unpublished case referred to them by Dr. Seaton Sailer. Recently, Zuelzer [11] published reports on two cases proved by necropsy, and Tomlinson [12] reported a case in which death was due to sickle cell anemia wherein accumulations of toxoplasmata were found in the brain and myocardium.

Of the group beyond infancy, Sabin,[13] who has contributed greatly to the knowledge of this disease, reported a fatal case of toxoplasmosis in a child. Pinkerton and his co-workers have reported two cases in adults who succumbed to a febrile illness similar to the "spotted fever" group,[14] and a third case from Peru [15] complicated by a Bartonella infection. Guimarães [16] reported a fatal case in an adult from Brazil.

The main contributors to knowledge in the field of human toxoplasmosis have been the groups associated with Wolf of New York and Sabin of Cincinnati, the former working primarily in the field of clinical medicine, the latter investigating laboratory methods of diagnosis and treatment. Wolf and his associates have described in detail the chorioretinitis and other ocular manifestations of toxoplasmic infection. They also described the multiple foci of intracerebral calcification demonstrable on roentgenographic examination as well as evidence of increased intracranial pressure, and in cases studied with pneumo-encephalography, an internal hydrocephalus. Using these findings in conjunction with laboratory methods of diagnosis, their cases include those finally studied at necropsy, as well as clinically accepted cases in which the patients are still alive.

Sabin and his associates early reported toxoplasmic infestation in animals in this country and noted that growth is possible only in living cells. In discussing the pathogenesis of this disease, Sabin stated that intracerebral inoculation of experimental animals resulted in spread of the organisms in the cerebrospinal fluid with marked periventricular tissue destruction. In several reported cases such localization of the reaction leads one to speculate as to whether the choroid plexus served as the initial site in the brain. Such localization was not evident in our case, all indications being that spread was by the blood stream, but some cysts were not related to, or even close to, blood vessels, thus suggesting possible transmission in migrating leukocytes. The histologic changes in this case indicate that the infection was still in the active invasive stage, the process of dissemination of the organisms still being in progress. No new light is thrown on the manner of infection or the portal of entry. The appearance of the lesions, location of the parasites, and complete absence of calcification in the brain lead us to believe that the infection was of short duration, either taking place, or being activated, only a few days before birth. As a matter of fact it cannot be definitely proved that infection did not occur during delivery or immediately thereafter.

We are in full agreement with Steiner and Kaump [10] in regard to the criteria for diagnosis. While conceding the desirability of extensive laboratory examinations on these cases, it seems plausible that cases exhibiting such remarkably distinctive inflammatory reactions and containing morphologically identical organisms should be classified as toxoplasmosis.

The differential staining qualities of the organism have been studied by Perrin [17] and should prove of value in establishing the diagnosis in questionable cases.

The occurrence of jaundice and extramedullary hematopoiesis in toxoplasmosis has been discussed by Steiner and Kaump [10] and by Zuelzer.[11] The former authors were able to make the diagnosis of erythroblastosis fetalis. The jaundice and degree of extramedullary hematopoiesis were impressive in our case, and from a histologic standpoint there is considerable evidence to support the diagnosis of erythroblastosis. However, stimulation of hematopoiesis in sites other than the bone marrow often occurs in the newborn infant due to a number of causes, including infection. Unfortunately, blood studies were not made during life in this case, and without such findings we hesitate to make an independent diagnosis of erythroblastosis until the general toxic effects of Toxoplasma are better understood.

Summary

The described case of toxoplasmosis occurring in a newborn infant is the first to be reported from the southeastern United States.

Toxoplasmata and accompanying lesions were found in the brain, spinal cord, heart, lungs, adrenals, stomach, pancreas, and diaphragm.

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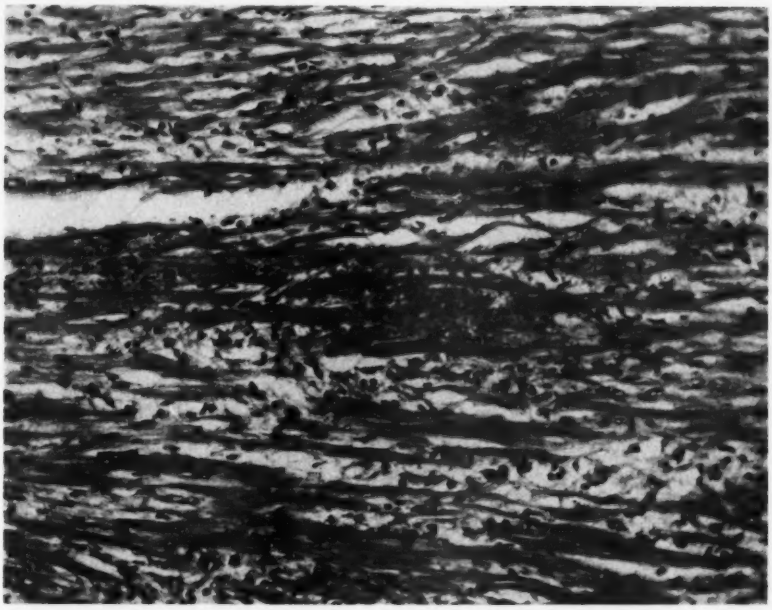
DESCRIPTION OF PLATES

PLATE 150

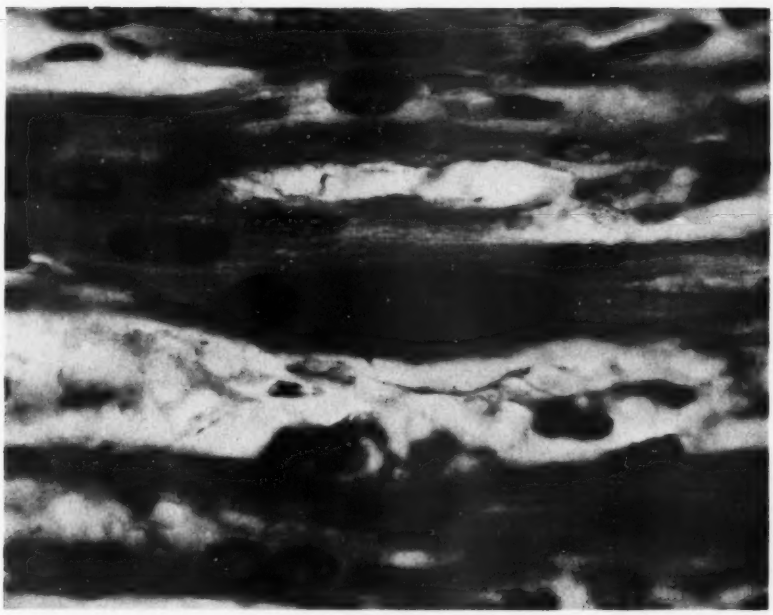
FIG. 1. Heavy inflammatory involvement of myocardium with focal necrosis. Phloxine and methylene blue stain. × 200.

FIG. 2. Accumulation of toxoplasmata in myocardium. Hematoxylin and eosin stain. × 1000.

1



2



Pratt-Thomas and Cannon Systemic Infantile Toxoplasmosis

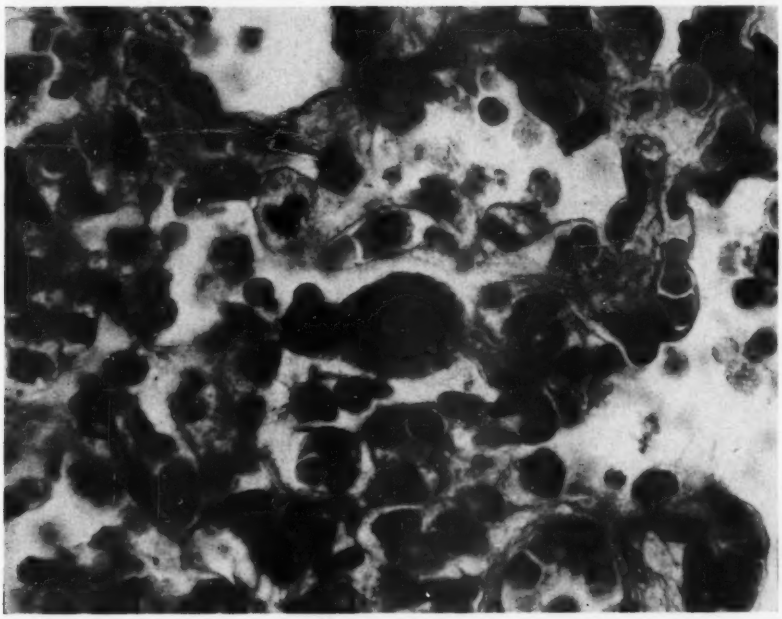
PLATE 151

FIG. 3. Small group of toxoplasmata in cardiac muscle. Hematoxylin and eosin stain × 1500.

FIG. 4. Accumulation of toxoplasmata in alveolar cell of lung. Hematoxylin and eosin stain. × 1000.

3

4



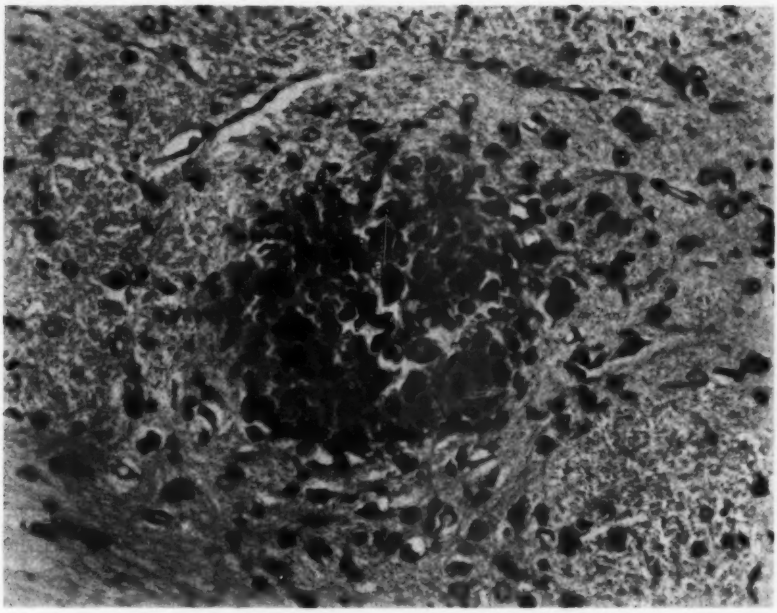
Pratt-Thomas and Cannon Systemic Infantile Toxoplasmosis

PLATE 152

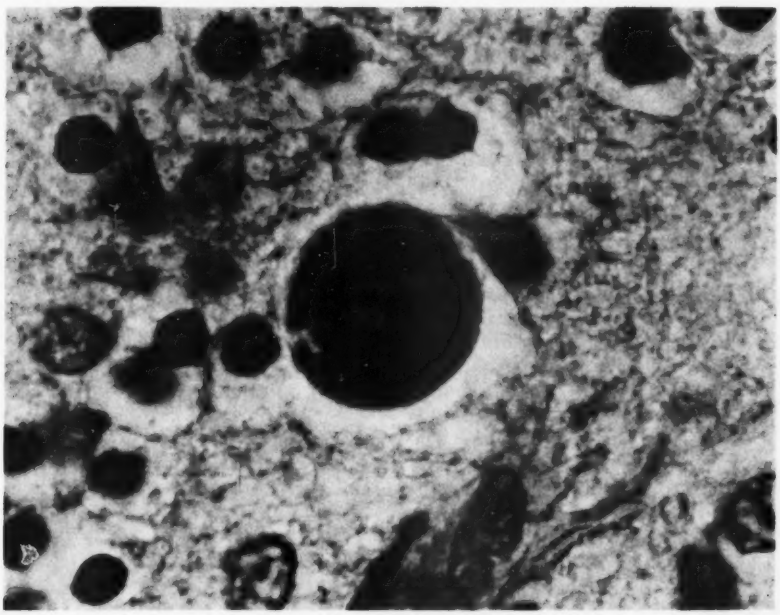
FIG. 5. Typical granuloma in brain. Hematoxylin and eosin stain. × 300.

FIG. 6. Toxoplasmic pseudocyst in brain. Hematoxylin and eosin stain. × 1500.

5



6



Pratt-Thomas and Cannon Systemic Infantile Toxoplasmosis

PATHOLOGIC FINDINGS IN THE LUNGS OF FIVE CASES FROM WHICH INFLUENZA VIRUS WAS ISOLATED *

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Reports in the literature of fatal cases from which influenza virus has been isolated are remarkably few, and still fewer are the descriptions of the pathologic changes in the lungs in such cases. We have been able to find only three such reports. The first case was described by Scadding [1] in 1937, the second by Stokes and Wolman [2] in 1940, and the third by Himmelweit [3] in 1943. The strain of influenza virus was not mentioned in Scadding's case. In Stokes and Wolman's case, it was influenza A (PR 8 strain). Himmelweit's case yielded an influenza virus closely related to, but not identical with, influenza B (Lee strain). All three cases were complicated by *Staphylococcus aureus* infection.

The pathologic change in Scadding's case [1] consisted of a necrotizing process involving the trachea, bronchi, bronchioles, and alveoli. The alveoli were filled with red blood cells, resembling an infarct. In limited areas there were small abscesses, 2 to 3 mm. in diameter.

In Stokes and Wolman's case [2] there was marked congestion of the alveolar capillaries. The alveoli were filled with edema fluid, red blood cells, and a few polymorphonuclear leukocytes. The septa were edematous and the lymphatics were filled with a serofibrinous exudate. Many lobules contained colonies of staphylococci with little or no leukocytic reaction about them. The bronchioles had lost their epithelium and their lumina contained mucus and leukocytic débris. The epithelium of the trachea and large bronchi had desquamated and had been replaced by a thick exudate of organizing fibrin and purulent material. The submucosa was thick, edematous, and congested, and was infiltrated with phagocytes, chiefly of the mononuclear variety.

In Himmelweit's case [3] the lungs showed bronchopneumonia, necrosis near the bronchioles, much hemorrhage, and many staphylococci. The epithelium of the trachea had been shed and there was a little fibrin on its surface with masses of cocci but only a few leukocytes. The bronchial epithelium had likewise desquamated.

In a fourth case reported by Wollenman and Finland [4] from the 1940–41 epidemic, the influenza virus was not isolated but evidence was given for its presence in the lung. A ferret inoculated intramuscu-

* Received for publication, August 4, 1945.

larly with a suspension of the lung of that case developed no signs of infection, but proved refractory to subsequent inoculation with influenza A (PR 8), and the ferret's serum taken prior to the second inoculation protected mice against infection with this strain of virus. This case, too, was complicated by infection with *Staphylococcus aureus* and the pathologic changes were very similar to those described by Stokes and Wolman.[2]

In addition to these four reports, Andrewes, Smith, and Stuart-Harris[5] recorded the isolation of influenza virus from the lungs of three cases of fulminating pneumonia which occurred during the 1936–37 epidemic in England and from which pure cultures of *Staphylococcus aureus* were obtained. One of these three cases is the same one that was reported by Scadding,[1] but the morbid anatomy of the lungs in the other two cases was not described.

We have had an opportunity to study the lungs from five cases from which an influenza virus was isolated. Two of the cases were unusual in that no significant pathogenic bacteria could be demonstrated, while of the other three, one was complicated by infection with *Staphylococcus aureus*, one by *Staphylococcus aureus* and *Streptococcus hemolyticus*, and one by Pneumococcus, type I.

The pertinent gross and microscopic findings, as well as the bacteriologic and viral studies, are given below.

Report of Cases

Case 1 *

A white woman, 26 years old, was admitted to the Faulkner Hospital on the afternoon of March 21, 1943. She had been in good health until the evening of March 18 when she had a rather abrupt onset of malaise, fever, restlessness, and insomnia. On the following day she had a slight sore throat with dysphagia and a harsh unproductive cough. On the afternoon of March 20 her temperature was 99.6° F. and her throat was very sore and slightly swollen but did not appear inflamed. At that time she began to have substernal distress with her cough. That night she became more restless. On the following morning the temperature was 100.6° F., pulse was 90, respirations were 28, and the patient was slightly cyanotic, somewhat stuporous, and complained of substernal oppression. That evening her temperature was 103.6° F.; pulse, 120; respirations, 42. The breath sounds in her lungs were diminished and a few râles were heard at both lung bases, but there were no signs of consolidation. She was sent to the hospital immediately.

On admission, there was slight injection of the pharynx, some hoarseness, and slight tenderness over the larynx. Examination of the lungs was negative except for a few scattered râles. The leukocyte count was 4,000 with a predominance of lymphocytes. Blood culture showed no growth. Urine was concentrated and showed a trace of albumin and a few white blood cells in the sediment.

The patient was given oxygen, sedation, and a total of 4 gm. of sufadiazine. She became increasingly cyanotic and her respirations more labored. She also com-

* Courtesy of Drs. A. A. Cushing and G. K. Mallory.

plained of more pain throughout the chest. The respirations sounded "moist" but there was very little cough or sputum. During the night, tracheal râles increased, and signs of consolidation and many râles were made out in the right lower chest. She died 12 hours after entry.

Post-Mortem Examination

Autopsy was performed 2 hours following death. The right pleural cavity contained approximately 100 cc., and the left approximately 300 cc. of serosanguineous fluid. The heart was negative.

The right lung weighed 740 gm. and the left, 1100 gm. The pleural surfaces of both lungs were smooth and glistening. The right lung anteriorly was salmon pink, soft and pillowy in consistence, and showed discernible alveolar detail associated with early emphysematous changes. There were three areas, 1 to 2 cm. in diameter, deep red and sharply demarcated from the surrounding lung tissue. Two of these were in the upper lobe and one in the middle lobe. These areas were subcrepitant and on section had a homogeneous red-purple color and exuded fluid blood on pressure. The posterior half of the right lung was boggy and subcrepitant to noncrepitant. The color was dark red to violaceous and was mottled by irregular areas of deeper purple-red. On section the cut surface was wet, oozed considerable blood, and presented irregular and rounded areas of deep purple, noncrepitant tissue from which dark, bloody fluid could be expressed. These areas bore no relationship to bronchi or bronchioles. The entire left lung had the same appearance externally and on section as the posterior half of the right lung. No pink, crepitant tissue was visible and both the upper and lower lobes had the consistence of liver tissue, although somewhat more friable and nodular. The trachea and major bronchi were filled with frothy fluid. The mucous membrane from the trachea to the tertiary bronchi was covered by a thin, yellow-gray, membranous exudate which could be peeled away only with difficulty to reveal an intensely congested, raw surface.

The spleen weighed 125 gm. and was not remarkable. The liver weighed 1700 gm. and appeared negative.

Microscopic Examination. In the lungs some alveoli were empty and appeared distended. Others contained edema fluid while still others contained red blood cells and varying numbers of polymorphonuclear leukocytes. In such alveoli there were masses of cocci. Others were filled with polymorphonuclear leukocytes and cocci. In addition, several small abscesses were present. Some of the alveolar capillaries were thrombosed. The bronchioles showed necrosis of their epithelium and of the underlying connective tissue which was infiltrated with numerous cells, some of which were polymorphonuclear

leukocytes, but many of which were so necrotic that their type could not be distinguished. The blood vessels of the bronchioles contained fibrin in their walls and some were thrombosed. The majority of the bronchioles were empty but a few contained red blood cells or polymorphonuclear leukocytes and cocci. There was a slight perivascular infiltration of some lymphocytes and plasma cells. Several medium-sized arteries contained thrombi. The pleura was edematous and the pleural lymphatics contained polymorphonuclear leukocytes and large mononuclear cells.

The epithelium of the trachea had been completely destroyed (Fig. 6). There was extensive necrosis involving the connective tissue of the wall of the trachea and of the leukocytes which had infiltrated it. Masses of cocci were present here. There were focal hemorrhages and deposits of fibrin. The majority of the blood vessels were partially or completely thrombosed. There was a marked infiltration of lymphocytes and plasma cells around the glands and between the smooth muscle fibers.

The heart was negative. In the spleen the histiocytes of the malpighian corpuscles were hyperplastic. The bone marrow showed maturation arrest of the granulocytic series, the majority of the cells being myelocytes with only an occasional adult polymorphonuclear leukocyte present.

Bacteriology. A hemolytic *Staphylococcus aureus* was obtained in pure culture from the heart's blood, lungs, right main bronchus, pleural cavities, and spleen.

Virus Studies. A filtrate of a 20 per cent suspension of the left upper lobe of the lung obtained at autopsy was used for virus studies. In the first attempt no lesions were obtained after ten intranasal passages in mice. Lungs of the third mouse passage, however, yielded virus when transmitted through eggs by allantoic inoculation. Allantoic fluid from subsequent egg passages produced fatal lesions in mice and agglutinated hen cells to a dilution of 1:256. This agglutination was inhibited by anti-PR 8 rabbit serum to a titer of 1:2048 and by anti-Lee serum to a titer of 1:8. Comparable inhibitions were obtained with PR 8 virus. Serum obtained from cardiac blood at autopsy gave no significant titer of antibodies for either PR 8 or Lee virus in complement fixation or agglutination inhibition tests.

Case 2

Case 2 has been reported elsewhere [6] because of the finding of acute nonbacterial myocarditis. The patient was a woman, 34 years of age, who had been in good health until the middle of December, 1942, when she had a mild attack of bronchitis or "flu." Cough and fatigue persisted thereafter but there were no positive

findings demonstrable by physical or roentgenological examination. On April 4, 1943, the patient noticed unusual fatigue and on the following morning she had generalized malaise and an increase in her cough which was unproductive. On April 6 she had chilly sensations, and on that evening her temperature was 103.4° F. but her lungs were still clear. On April 9 her condition became much worse; the temperature was 102.6° F.; pulse was 124, feeble and thready, and the blood pressure was 125/78 mm. Hg. There were suggestive signs of consolidation of the right lower lobe and a few scattered râles in both lung bases. Heart sounds were faint and distant. The white blood count was 20,000, of which 70 per cent were polymorphonuclear leukocytes. The urine showed 2 plus albumin and a few white blood cells. Sputum could not be obtained but a throat culture yielded a scant growth of *Neisseria catarrhalis* and a few colonies of *Staphylococcus aureus*.

The patient was given 4 gm. of sulfadiazine and 1 gm. every 4 hours thereafter. She received a total of 8 or 9 gm. The signs and symptoms thereafter were those of increasing cardiac embarrassment and she was admitted to the Peter Bent Brigham Hospital late in the afternoon of April 10. A bedside roentgenogram of her chest at that time showed irregular mottling extending out from both hilar regions and a small amount of fluid in the axillary region. An electrocardiogram showed complete heart block and bizarre ventricular complexes. In spite of oxygen therapy and digitalis, the patient continued a downhill course and died 7 hours after admission.

Post-Mortem Examination

Autopsy was performed 8 hours after death. The right pleural cavity contained 950 cc. of a pale yellow fluid with flecks of fibrin, and the left contained 600 cc. of a similar fluid. There were several old fibrous adhesions binding the anterior and lateral surfaces of the right lung to the chest wall. Elsewhere the pleural surfaces of both lungs were smooth and glistening. The heart weighed 480 gm. The myocardium was light pink. Both the right and left ventricles were increased in thickness, the right measuring 0.8 and the left 2.0 cm. The valves were negative.

The lungs were somewhat heavier than normal. They were fairly crepitant throughout save at the bases where diminution in crepitation was more marked. Bloody fluid could be expressed from the cut surfaces. No areas of consolidation were present. The bronchial mucosa was slightly reddened but was glistening and free from exudate. The trachea appeared normal. There was no secretion or exudate present.

The spleen weighed 120 gm. Its architecture was well preserved and only a small amount of pulp could be scraped away. The liver weighed 1700 gm. and was negative. Bone marrow expressed from a rib was copious and deep red.

Microscopic Examination. The lungs showed a considerable degree of congestion. The alveoli contained a moderate number of large mononuclear cells, many of which had phagocytized carbon. Sections from the right lower lobe showed a perivascular infiltration of a few lymphocytes, plasma cells, eosinophils, and an occasional mast cell

(Fig. 2). One focus of acute inflammation was found in a section from this lobe (Fig. 1). Here several alveoli contained fibrin, large mononuclear cells, lymphocytes, and polymorphonuclear leukocytes. The walls of these alveoli contained cells of the same type. There was also swelling of the alveolar lining cells. A section from the left upper lobe likewise showed an acute inflammatory lesion in which the alveoli contained polymorphonuclear leukocytes, fibrin, and some large mononuclear cells. Stains for bacteria failed to reveal any microorganisms in these acute lesions or elsewhere. The epithelium of the bronchioles was unaffected. Their walls were infiltrated with a few lymphocytes, plasma cells, and a rare polymorphonuclear leukocyte. The heart showed extensive necrosis of muscle fibers with interstitial infiltration of lymphocytes, plasma cells, some large mononuclear cells, and an occasional eosinophil and mast cell. The spleen showed hyperplasia of the histiocytes in the malpighian corpuscles. In some areas of the liver there was central necrosis. The hepatic cells throughout showed fatty as well as hydropic degeneration. The bone marrow was not remarkable.

Bacteriology. Cultures of the heart's blood, lungs, and serous cavities yielded no growth.

Virus Studies. A Berkefeld V filtrate of a 20 per cent suspension of part of the right lower lobe was used for virus studies. The first attempt in mice was abandoned after six intranasal passages failed to produce pulmonary lesions. In the second attempt a different portion of the same lung was used, lesions appeared in the second passage, and death occurred on the fourth and subsequent passages. Survivors of the third passage were later given a challenge dose of 100 lethal doses of PR 8 and survived. In eggs, the virus became well established by the sixth passage. The allantoic fluid of later passages agglutinated hen cells up to a dilution of 1:2048. This agglutination was inhibited by anti-PR 8 rabbit serum to a titer of 1:1024, and by anti-Lee rabbit serum to a titer of 1:32. The patient's own serum obtained before death failed to fix complement or inhibit hen cell agglutination with PR 8 virus.

Case 3 *

The patient was a white, single office worker, 18 years old, who was admitted to the Evans Memorial Hospital at 4:00 p.m. on December 13, 1943. Her illness had begun abruptly at 3:00 p.m. on December 11, when she noted a sore throat and dysphagia. On the following day a physician found her temperature to be 101° F. and told her she had a bad sore throat and prescribed cough medicine. She had anorexia and vomiting that day and felt somewhat drowsy. At 1:00 a.m. on the morning of admission she developed severe pains across her lower chest and a slight cough productive of a small amount of sputum. She was given four sulfonamide

* Courtesy of Drs. Chester S. Keefer and John J. Curry.

tablets but soon became delirious and her physician sent her into the hospital after making a diagnosis of pneumonia.

On admission she appeared critically ill, toxic, cyanotic, delirious, dyspneic, and semicomatose. She was unresponsive, and incontinent of urine and feces. Temperature was 106.6° F. (rectal); pulse, 175; respirations, 53; blood pressure, 60/40 mm. Hg. She was well developed but poorly nourished. Her skin was hot and dry and she was markedly dehydrated. The mouth and tongue were very dry with thick, yellow, ropey material at the base of her tongue. Her pharynx was deeply injected. There was slight dullness at the base of the right lung posteriorly where the breath sounds were suppressed. A few fine, crepitant râles were heard there and in the right posterior axillary region. The lungs were otherwise clear. The heart sounds were rapid, faint, and distant. The hemoglobin was 10 gm.; red blood count, 4.86 million; white blood count, 1,350, with 24 per cent polymorphonuclear leukocytes, 72 per cent lymphocytes, and 4 per cent monocytes. A throat smear showed gram-positive diplococci and culture of the sputum yielded beta hemolytic streptococci and hemolytic *Staphylococcus aureus*. The latter also was grown from the blood culture. A portable roentgenogram of the chest showed large patches of dense infiltration in all but the upper part of the right lung field and a few similar patches were noted in the left mid-lung field.

Oxygen therapy was started at the time of entry and the patient was given an intravenous infusion of 1200 cc. of 5 per cent glucose in saline solution to which 5 gm. of sodium sulfadiazine had been added. The cyanosis improved somewhat and the blood pressure rose temporarily to 90/60 mm. Hg. The patient remained stuporous and combative. The râles in her chest increased and loud tracheal rhonchi were heard. The blood pressure soon dropped again and the pulse became thready and imperceptible. She became extremely restless and had a slight convulsive seizure with muscular twitchings of her face. Bloody foam exuded from her mouth and she expired about 3 hours after admission.

Post-Mortem Examination

Autopsy was performed 3 hours following death. The mucosa of the oropharynx and larynx was markedly reddened. Each pleural cavity contained approximately 500 cc. of slightly turbid, yellow, watery fluid. The pleural surfaces were smooth, dull, and bright red-gray. The heart weighed 225 gm. and was negative.

The right lung weighed 900 gm. and the left, 730 gm. The lungs were soft, boggy, and subcrepitant with only a few slightly firmer areas suggesting consolidation. On section, the alveolar architecture was obscured by a dark crimson background from which a large amount of frothy, serosanguineous fluid could be expressed. No definite consolidation could be found. The trachea and bronchi, which were filled with frothy, serosanguineous fluid, were lined with a dull, dark crimson mucosa which appeared to be extensively and superficially eroded. The hilar lymph nodes were enlarged and soft.

The spleen weighed 140 gm. The malpighian corpuscles were well defined against a dark crimson background. A large amount of soft pulp could be scraped away. The liver weighed 1280 gm. and was not remarkable.

Microscopic Examination. Sections from the lungs showed a variety of changes. In some there was intense congestion and the alveoli contained edema fluid, red blood cells, a few large mononuclear cells, and a rare polymorphonuclear leukocyte. In addition, there was a hyaline membrane, often appearing somewhat fragmented, lining some of the alveolar ducts and alveoli. The bronchioles in these areas contained edema fluid, numerous red blood cells, and large mononuclear cells. In addition, there was abscess formation. At the periphery of the abscesses, the intra-alveolar hemorrhages were more extensive and there was also a deposit of fibrin. The blood vessels here contained thrombi. Some bronchioles showed necrosis of their epithelium and contained in their lumina polymorphonuclear leukocytes, large mononuclear cells, red blood cells, and cocci. The walls of the bronchioles were infiltrated with large mononuclear cells and polymorphonuclear leukocytes. Gram-positive cocci, growing both in clusters and in long chains, occurred in all sections but were especially numerous in the abscesses and in the bronchioles that showed necrosis of their mucosa. In some sections the pleura was covered with a thin layer of fibrin.

The heart showed a few scattered, large mononuclear cells and lymphocytes in the interstitial tissue of the myocardium. In the adrenal cortex there were several foci of necrosis in which the necrotic cells had been invaded by polymorphonuclear leukocytes. The bone marrow showed numerous myelocytes but only rare adult granulocytes.

Bacteriology. Hemolytic *Staphylococcus aureus* and *Streptococcus hemolyticus* were cultured from the pericardial cavity, the upper and lower lobes of the right lung, the lower lobe of the left lung, the right and left bronchi and both pleural cavities.

Virus Studies. A 20 per cent suspension of a portion of the hemorrhagic lung was passed through a Berkefeld V filter and the filtrate used for inoculation of mice and of chick embryos. No transmissible lesions were found in the mice after six intranasal passages, and further attempts were abandoned. The first intra-allantoic inoculation, however, yielded virus recognizable by moderate agglutination of the erythrocytes of the embryo as the allantoic fluid was withdrawn. Fifth passage allantoic fluid, diluted 1:10, regularly produced deaths with typical lesions in mice, and these were completely prevented by simultaneous inoculation of anti-influenza A (PR 8) ferret serum but were unaffected by similar amounts of anti-influenza B (Lee) ferret serum. This virus behaved in an atypical manner in agglutination-inhibition tests. With anti-PR 8 rabbit serum inhibition occurred in a titer of 1:64, and with anti-Lee serum in a titer of 1:32. Further studies of this virus are in progress.

Case 4

Case 4 was also included in a previous report[6] because of small myocardial lesions found at autopsy. The patient was an Italian iron worker, 39 years of age, who was admitted to the Boston City Hospital on January 31, 1944, complaining of dyspnea and hemoptysis of 2 days' duration. He denied having had cardiorespiratory symptoms until January 23 when he had a slight "head cold" which was followed by malaise, anorexia, and prostration. On January 26, he had severe shaking chills followed by fever. Three days later he began to have marked dyspnea, cyanosis, and cough, and raised grossly bloody sputum. He also had two attacks of substernal pain.

When he arrived at the hospital the patient was markedly cyanotic and dyspneic and had audible tracheal râles. He was coughing and expectorating dark red blood. The temperature was 98.4° F., pulse was 100 and regular, and respirations were 28 and labored and had a prolonged expiratory phase. The blood pressure was 138/88 mm. Hg. In both lungs there were numerous medium and coarse, moist râles but no definite signs of consolidation. The leukocyte count was 19,000 of which 88 per cent were polymorphonuclear leukocytes, and the hemoglobin was 96 per cent. The nonprotein nitrogen of the blood was 135 mg. per 100 cc. A smear of sputum showed gram-positive cocci and bacilli. An electrocardiogram showed left axis deviation but no other significant abnormality. A bedside roentgenogram of the chest showed diffuse clouding of both lung fields with irregular, fluffy areas of density. The patient failed to respond to therapy with oxygen and other supportive measures and died 14 hours after entry.

Post-Mortem Examination

Autopsy was performed 14 hours after death. The surfaces of the pleural cavities were smooth and glistening. The right cavity contained 600 cc. of a reddish, straw-colored fluid; the left, 500 cc. of a similar fluid. The heart weighed 330 gm. The coronary arteries showed atheromatous changes but were not occluded. There was a fibrous scar about 2 cm. in diameter in the interventricular septum.

The right lung weighed 1250 gm. and the left, 1100 gm. Their surfaces were glistening and transparent. Both lungs were subcrepitant throughout. On section, no discrete areas of consolidation were present but all lobes felt much firmer than normal. The trachea and bronchi contained a slightly mucoid, serosanguineous fluid.

The spleen weighed 105 gm. The cut surface was purplish red and the malpighian corpuscles were poorly delineated. The liver weighed 1690 gm. and cut with some increased resistance. The kidneys each weighed 205 gm. and were not remarkable save for a moderate degree of congestion.

Microscopic Examination. The heart showed large areas of scarring of the myocardium. In addition, there was necrosis of scattered muscle fibers and an interstitial infiltration of large mononuclear cells, lymphocytes, plasma cells, eosinophils, and polymorphonuclear leukocytes.

All lobes of the lungs showed essentially the same histologic picture. Some alveoli contained large mononuclear cells, many of which had

phagocytized carbon. In other alveoli there was edema fluid, a few red blood cells, delicate strands of fibrin, and varying numbers of polymorphonuclear leukocytes (Fig. 4). Numerous alveolar ducts and alveoli were lined with a dense, acidophilic, hyaline membrane in which were often embedded particles of carbon, polymorphonuclear leukocytes, and large mononuclear cells (Fig. 3). Some of the ducts and alveoli lined with this membrane were empty; others contained edema fluid and strands of fibrin. There were a moderate number of alveoli in foci which contained polymorphonuclear leukocytes, large mononuclear cells, and fibrin. The alveolar capillaries contained an increased number of polymorphonuclear leukocytes, especially those adjacent to the hyaline membrane. Thrombosis of the capillaries was seen occasionally. The epithelium of the bronchioles was intact. Some of the bronchioles were empty; others contained mucus, polymorphonuclear leukocytes, red blood cells, and fibrin. Their walls were infiltrated with fairly numerous polymorphonuclear leukocytes, lymphocytes, a few plasma cells, and a rare mast cell. The septa were markedly edematous and their lymphatics were dilated. Some of the septa were infiltrated with large mononuclear cells, lymphocytes, plasma cells, and polymorphonuclear leukocytes. Stains for bacteria failed to reveal microorganisms in any section.

The spleen showed in the larger veins a subendothelial infiltration of a few lymphocytes and plasma cells. The liver cells in the centers of the lobules had been replaced by large mononuclear cells, lymphocytes, and a few eosinophils. In the kidneys, some tubules contained necrotic epithelial cells in their lumina and such tubules were lined with flattened epithelium in which an occasional mitotic figure was present. There was an interstitial infiltration of lymphocytes, plasma cells, and eosinophils. The bone marrow was essentially normal.

Bacteriology. Cultures of the various lobes of the lungs showed no growth. An unidentified gram-negative diplobacillus was cultured from the heart's blood and a gram-negative diplococcus from the spleen. Both of these organisms were considered to be contaminants.

Virus Studies. A sterile filtrate of a 20 per cent suspension of some hemorrhagic lung tissue was used for virus studies. Typical lesions appeared in mice on the sixth intranasal passage and deaths occurred regularly beginning with the seventh. Neutralization tests with the mouse lung suspensions and immune ferret serums showed definite protection by anti-PR 8 serum and none by anti-Lee serum. Virus was recognized in the allantoic fluid of the first eggs inoculated with the filtered lung suspension. The fluid from the ninth passage agglutinated hen cells up to a dilution of 1:512 and this agglutination was inhibited

by anti-PR 8 ferret serum to a titer of 1:1024 and by anti-Lee serum to a titer of 1:64. Serum obtained from the patient before death had no significant antibodies for the PR 8 or Lee viruses.

Case 5

A white painter, 61 years old, was admitted to the Boston City Hospital on March 6, 1944, too ill to answer questions. From his wife and sister it was learned that he had always been in good health except for childhood diseases and an attack of rheumatic fever in 1902, from which he recovered without recurrences or sequellae. For 2 months preceding the present illness he had seemed unusually tired but had improved and felt perfectly well during the week prior to entry. On March 3, at 3:00 p.m., while at work he had a shaking chill and went home feeling feverish and weak. He went to bed and on the following day had chilly sensations, pleuritic pain in the right lower chest, and cough productive of large amounts of dark, rusty sputum. A physician found his temperature on that afternoon to be 103° F. and diagnosed "grippe." His cough and chest pain increased in severity and on the morning of admission he was having drenching sweats.

On admission he appeared severely ill, markedly dyspneic, cyanotic, and dehydrated. His temperature was 103° F.; pulse, 136; respirations, 42; blood pressure, 158/78 mm. Hg. He was coughing and raising rusty sputum and obviously having pain with respiration. The throat was injected and covered with a mucoid exudate. Respiratory movements were limited, particularly on the right. There was dullness to flatness over the right lower lung posteriorly and crepitant râles were heard over this area and in the right axilla, but the rest of the lungs seemed clear. The heart sounds were rapid but regular. Hemoglobin was 95 per cent; white blood count, 2,000, with 60 per cent polymorphonuclear leukocytes, many of them band forms. Type I pneumococci were identified in his sputum by the Neufeld method and the same organism was obtained from the blood cultures. The urine was concentrated and showed 4 plus albumin, occasional white blood cells, and numerous granular casts. The nonprotein nitrogen of the blood was 45 mg. per 100 cc. and the Hinton test on the blood was negative.

Oxygen therapy was begun on admission and an intravenous infusion of 15,000 cc. of saline solution containing 5 gm. of sodium sulfapyrazine was given. Antipneumococcus serum was also given intravenously in amounts of 1, 5, and 14 cc. at approximately 2-hour intervals, a total of 200,000 units being given between 5 and 11 p.m. There were no immediate untoward effects and there was a slight decline in the temperature and pulse rate during this treatment. About 1 hour after the last dose, however, the patient's condition became very poor, the blood pressure dropped rapidly despite coramine and caffeine, and he died about 40 minutes later.

Post-Mortem Examination

Autopsy was performed 9 hours following death. The right pleural cavity contained approximately 500 cc. of cloudy, yellow fluid. There were friable, fibrinous adhesions to the whole lower lobe and to the diaphragm. The left pleural cavity contained no excess fluid and the pleural surfaces were smooth and glistening.

The heart weighed 400 gm. and showed changes consistent with arteriosclerotic heart disease.

The right lung weighed 1910 gm. The upper and middle lobes were deep red while the lower lobe was yellow. The consistence of the lower

lobe was firm and noncrepitant. On section, a yellow-pink material gushed forth. The cut surface was roughened and showed no discrete, firm, or raised areas. The bronchioles exuded a yellow, purulent material on pressure. The upper and middle lobes were crepitant. On section, pink, watery fluid exuded. The cut surface was uniformly soft and wet. The bronchioles contained pink, watery fluid. The left lung weighed 820 gm. It resembled the upper and middle lobes of the right lung, both externally and on section. The trachea and major bronchi contained a watery, pink, frothy fluid. The mucosa of the trachea and bronchi was injected but was intact. The spleen weighed 265 gm. and was soft. The liver was slightly enlarged, weighing 2100 gm.

Microscopic Examination. In the heart there were some focal collections of large mononuclear cells in the interstitial tissue of the myocardium.

In the lungs, sections of the right upper lobe showed the majority of the alveoli to contain edema fluid and a varying number of carbon-filled, large mononuclear cells. Some alveoli were considerably distended. The epithelium of the bronchioles was intact (Fig. 5). Some bronchioles were empty; others contained edema fluid. In sections of the right lower lobe the alveoli contained some large mononuclear cells and numerous polymorphonuclear leukocytes, many of which were necrotic. Many alveoli also contained fibrin adjacent to their walls, while there was little or none in the central portions of their lumina. In places, the alveolar capillaries were congested; in others they were thrombosed. The pleura was covered with a layer of fibrin beneath which were fairly numerous polymorphonuclear leukocytes. The left upper lobe was essentially negative save for some distended alveoli. The left lower lobe was similar to the right upper lobe. In addition, several alveoli contained a few polymorphonuclear leukocytes, large mononuclear cells, and a small amount of fibrin. The epithelium of the bronchioles was intact. Their walls were infiltrated with numerous lymphocytes and plasma cells. Their lumina contained edema fluid and a few polymorphonuclear leukocytes. Numerous gram-positive diplococci were present in the alveoli of the upper and lower lobe of the right lung and in the lower lobe of the left. In the upper lobe of the left lung similar microorganisms were seen only in the alveolar capillaries.

The bone marrow revealed numerous myelocytes but only rare adult leukocytes.

Bacteriology. Pneumococcus, type I, was grown from the heart's blood and from all lobes of the right lung, and the lower left lobe.

Virus Studies. A portion of the right upper lobe was taken under

sterile precautions and preserved at —70° C. for virus studies. A 20 per cent suspension of sterile filtrate was used for intranasal inoculation of mice and intra-allantoic inoculation of chick embryos. Lesions appeared in the lungs of mice on the second passage and deaths occurred in the third and subsequent passages. There was slight agglutination of the embryonic erythrocytes in the allantoic fluid of the first egg passage and strong agglutination in subsequent passages. In a preliminary neutralization test the virus produced fatal lesions regularly in mice and these were prevented by the use of anti-influenza A ferret serum diluted 1:50 but not by similar amounts of anti-influenza B serum. Serum obtained from the patient on admission was used in agglutination-inhibition tests and gave a titer of 1:64 with influenza A (PR 8), 1:256 with influenza B (Lee), and 1:256 with the patient's own virus.

Summary of Pathologic Findings

It will be noted from the above data that two of the cases (2 and 4) were uncomplicated by bacterial infections. In case 2, death resulted from cardiac failure associated with an extensive acute myocarditis. The changes in the lungs were surprisingly slight and consisted of acute lesions involving a few alveoli. The bronchioles were unaffected. In case 4, death was due to the pulmonary involvement. The lungs in this case showed edema, some alveolar hemorrhages, fibrin, and extensive formation of a hyaline membrane. The epithelium of the bronchioles was intact but their walls were infiltrated with cells of various types. Their lumina were empty or contained mucus, leukocytes, red blood cells, and fibrin. There was marked edema of the septa.

Case 1 was complicated by a fulminating *Staphylococcus aureus* infection, causing an extensive necrotizing process involving the trachea, bronchi, and bronchioles. The alveoli showed edema, hemorrhages, an exudate of polymorphonuclear leukocytes, and abscess formation.

In case 3 an attack of influenza was complicated by a secondary infection with a beta hemolytic streptococcus and a hemolytic *Staphylococcus aureus*. The lungs showed alveolar hemorrhages, edema, and hyaline membrane formation in some sections. In others there was abscess formation. The epithelium of the bronchioles was intact in the former areas and necrotic in the latter. There was in addition an acute fibrinous pleuritis.

Case 5 was complicated by a pneumococcal pneumonia of the right lower lobe and a pneumococcal bacteremia. The right lower lobe showed a resolving lobar pneumonia. The right upper and left lower lobes showed edema and, in addition, in the left lower lobe several alveoli contained polymorphonuclear leukocytes, large mononuclear

cells, and fibrin. The bronchiolar epithelium in all lobes was intact. Bronchiolar walls were infiltrated with lymphocytes and plasma cells. There was an acute fibrinous pleuritis of the right lower lobe.

Correlation of Pathologic Changes and Virus Studies

In each case, material from only one lobe was utilized for the isolation of the virus. In case 1, unfortunately no note was made as to which lobes the microscopic sections represented. In case 2, the virus was isolated from the right upper lobe and histologically the only lesions present were focal lesions involving a few alveoli and consisting of an exudate of polymorphonuclear leukocytes, fibrin, and some large mononuclear cells. In case 3, no record was kept as to which lobe was studied for the presence of a virus. In case 4, likewise, no such record was kept, but the process was uniform throughout all lobes and it would seem justifiable to assume that the changes described, namely, edema, alveolar hemorrhages, fibrin, and hyaline membrane formation, represent the reaction to the virus. It should be noted that the bronchiolar epithelium was intact in this case as it was in case 2. In case 5, virus was isolated from the right upper lobe and sections from this lobe showed edema of the alveoli with an exudate of a moderate number of large mononuclear cells. As in cases 2 and 4, the bronchiolar epithelium was unaffected.

The fact that a virus was found in a single lobe in each instance is, of course, no indication that it was not present in some, if not all, of the other lobes. However, due to practical difficulties it was impossible to utilize more than one lobe from each case for virus studies.

Comment

As was indicated earlier in this paper, the number of fatal cases in which influenza virus has been demonstrated and the pathologic changes described is remarkably small. Only four cases with pathologic descriptions of the lungs have been found by us in the literature. We have had an opportunity to examine five additional cases and these form the basis of this report.

It appears of no value to discuss the pathologic changes which have been described in previous pandemics and epidemics of influenza for nothing is known as to the etiologic agent. With a very rare exception, all such cases were complicated by secondary bacterial infections and the pathologic lesions described were caused for the most part, if not entirely, by such secondary invaders. Goodpasture [7] described two cases which were bacteria free. His first patient died 7 days after the

initial symptoms and 2 days after signs of consolidation appeared in the lungs. Microscopic examination of the lungs showed injury and destruction of the alveolar walls with hemorrhage, edema, a little fibrin, and scant cellular exudate. The alveolar ducts were dilated and some of them showed a hyaline membrane on their walls. His second case was of a subacute type with a terminal exacerbation. Microscopically, the lungs showed alveolar hemorrhages, innumerable foci of polymorphonuclear leukocytes, fibrin, large mononuclear cells, disintegrating hyaline material, and small areas of necrosis of the alveolar walls. In some areas there was a thick layer of hyaline material on the walls of dilated ducts and alveoli. The epithelial lining of the large and small bronchi was intact. In certain respects these two cases resemble histologically our case 4 which was likewise bacteria free.

In our series, two cases were bacteria free and three were complicated by secondary bacterial infections.

Much emphasis has been placed in the past on necrotizing bronchiolitis as a feature of influenza. Such a process also has been found in experimental infections with influenza virus in mice and ferrets. However, in our two cases which were not complicated by bacteria the epithelium of the bronchioles was unaffected. This was also true of Goodpasture's case [7] in which he described the bronchioles. Furthermore, in our cases complicated by secondary bacterial invaders, the bronchioles in the portions of the lung which were not involved by the bacterial infection but which contained the virus were unaffected.

From our series of cases it would seem that it would be difficult to recognize changes produced by the virus in the presence of bacterial infections. It is possible that more definite lesions due to the virus had not been produced because of the short duration of the disease in these cases—2 to 3 days. It will be noted from the descriptions of the histologic changes in our cases that the lesions in four of the five cases were minimal. However, it is entirely possible that if it had been practicable to make multiple sections of each lobe, more severe lesions might have been found. A similar situation was true with the virus studies. In each case, tissue from only one lobe was tested for the presence of virus. Another explanation of the lack of severity of the lesions is the short course of the disease in the three cases complicated by secondary bacterial invaders. Death in these cases may well have been due primarily to the bacterial infections. In case 2, in which the pulmonary lesions were minimal, the duration of the disease was probably 7 days and death was due to acute myocarditis. The lesions in this case may represent a minimal infection with virus or possibly a late stage. The

TABLE I

Certain Relevant Data in Five Cases in Which Influenza Virus Was Recovered from the Lungs

Case number	1	2	3	4	5
Sex and age (years)	Female, 26	Female, 34	Female, 18	Male, 39	Male, 61
Dates: Admission	3/21/43; 9 P.M.	4/10/43; 6 P.M.	12/13/43; 4 P.M.	1/31/44; 4 P.M.	3/6/44; 3 P.M.
Onset of influenza	3/18; P.M.	4/4; P.M.	12/11; 3 P.M.	1/23	3/3; P.M.
Onset of pneumonia	3/20; P.M.	4/6 or 4/9(?)	12/13(?); 1 A.M.	1/26 or 1/29	3/4
Death	3/22; 8 A.M.	4/11; 1 A.M.	12/13; 7 P.M.	2/1; 1 A.M.	3/7
Pulmonary involvement					
Clinical: Consolidation	R.l.	R.l.(?)	Patchy R. and L.	0	R.l.
Râles	Bilateral	R.l., L.l.	Bilateral	Bilateral	R.l., m.
X-ray: Consolidation		0	0	0	
Mottled density		Mid-lungs	Bilateral	Bilateral	
White blood cell count					
Number per cmm.	4,000	20,000	1,350	19,000	2,000
% polymorphonuclear cells	40	70	24	88	60
Bacteriology					
Sputum			S. au.; Str. B	Negative	Pn. I
Blood (ante-mortem)	No growth	No growth	S. au.	No growth	Pn. I
Cardiac blood (autopsy)	S. au.	No growth	No growth	G— Bact. (contam.)	Pn. I
Lungs (autopsy)	S. au.	No growth	Str. B; S. au.	No growth	Pn. I
Others (autopsy)	P.F.; S. au. Bronchus; S. au.	P.F.; no growth	P.F.; Str. B. and S. au. Bronchus; St. B. and S. au.		P.F.; Pn. I
Virus isolation					
Source	Lung (Lu)	Lung (R.l.)	Lung	Lung	Lung (R.u.)
Result in mice	Influenza A	Influenza A	Negative	Influenza A	Influenza A
Result in chick embryos	Influenza A*	Influenza A	Influenza A(?)	Influenza A	Influenza A

Abbreviations: R. = right; L. = left; l. = lower; m. = middle; u. = upper lobe.
S. au. = Hemolytic *Staphylococcus aureus;* Str. B. = Beta hemolytic streptococci.
Pn. I = Type I pneumococcus; P.F. = pleural fluid; G— = gram negative.

* Obtained by allantoic inoculation of a suspension of lung from the third mouse passage in this case. Others obtained from direct inoculation of the eggs with original lung suspensions.

fourth patient (case 4) lived 9 days and died of pulmonary involvement due to virus alone. The histologic changes, in our opinion, represent the typical picture of a pure influenza virus pneumonia.

Some of the relevant data in the five cases are summarized in Table I. It is seen that the three cases infected with bacteria showed a marked leukopenia. In these cases the bone marrows show maturation arrest of the granulocytic series. In the two bacteria-free cases, leukocytosis was present and the bone marrows were normal. The leukopenia may be attributed to the short course of the disease or to a depressant action of the bacteria. However, it appears that the uncomplicated influenza virus infections were accompanied by leukocytosis rather than leukopenia.

Because of the difficulties usually encountered in isolating an influenza virus from fatal cases as compared with the relative ease with which they were obtained by mouse and chick embryo inoculation and by passage from these cases and from other non-fatal cases,[8] the possibility must be considered that the viruses isolated from the present cases may not have originated from these lungs but have occurred as laboratory contaminants.[9] Such a possibility is extremely unlikely. The viruses in the first two cases were each isolated at a time when no other influenza virus was available in the same laboratory. In the case of the other strains, evidence for the presence of the virus was obtained after the original allantoic inoculation in each instance, and then increased with further passages. Mouse inoculation and passage of the same lung suspensions were successful in only two of the three cases. Furthermore, the virus in one of these cases was serologically distinct from the others. In addition, unsuccessful attempts were made by similar passages in mice and eggs obtained from the same sources to isolate viruses from nine other fatal cases of influenza and atypical pneumonia.

Summary

1. The pathologic changes have been described in five cases in which influenza virus was obtained from the lungs. Only three earlier reports in which the structural changes were described have been found in the literature.

2. Two of our cases were bacteria free; the other three had secondary bacterial invaders.

3. One of the bacteria-free cases showed pathologic changes which were considered typical of influenzal pneumonitis. These consisted of edema, alveolar hemorrhages, fibrin, and the formation of a hyaline membrane.

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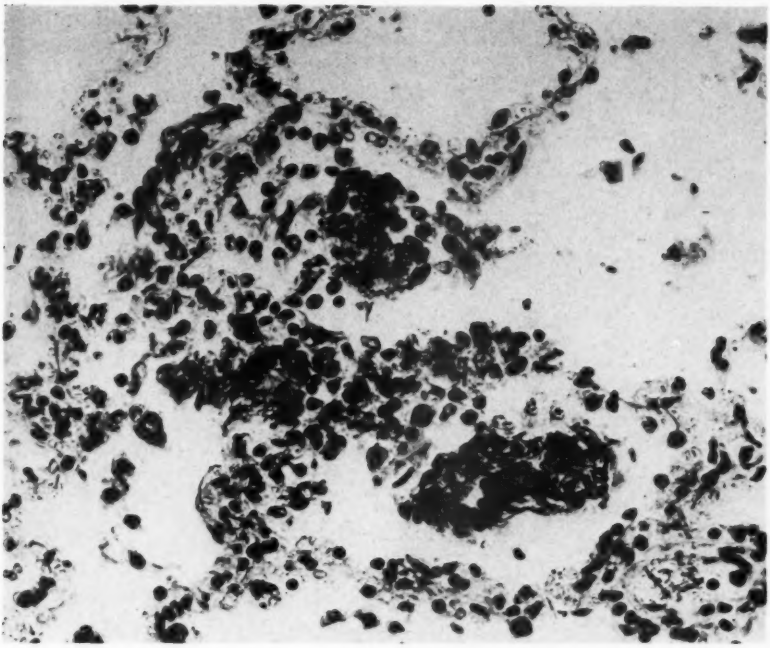
DESCRIPTION OF PLATES

PLATE 153

FIG. 1. Case 2. Acute focal lesion in the right lower lobe. The alveoli contain fibrin, large mononuclear cells, lymphocytes, and polymorphonuclear leukocytes. There is also swelling of the cells lining the alveoli. Phloxine-methylene blue stain. × 150.

FIG. 2. Case 2. Right lower lobe. Perivascular infiltration of lymphocytes and plasma cells. Phloxine-methylene blue stain. × 150.

1



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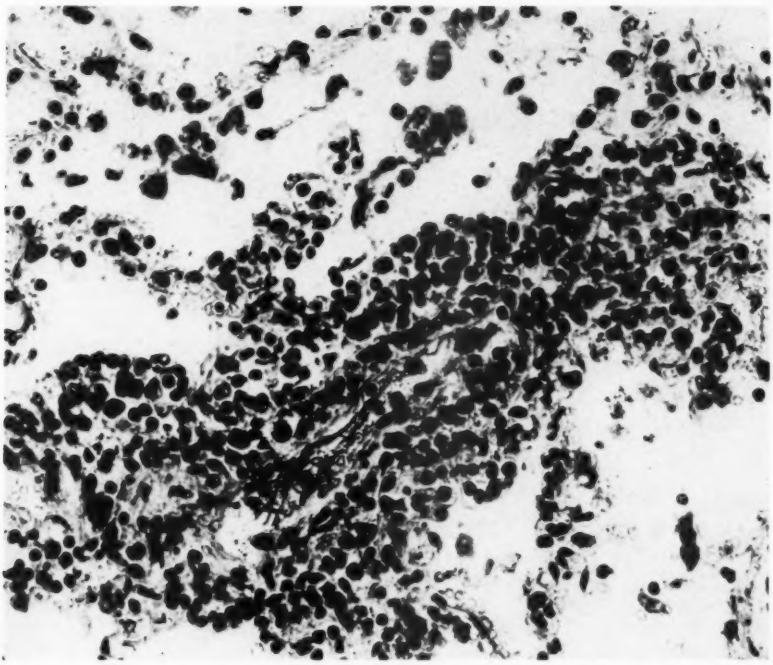

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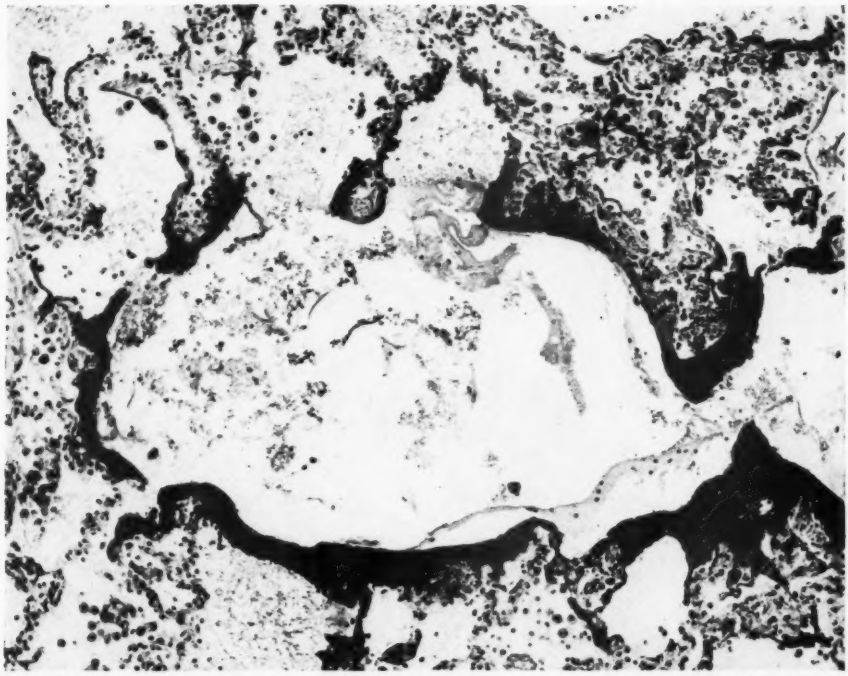
PLATE 154

FIG. 3. Case 4. Dilated alveolar duct lined with dense, hyaline membrane. Phloxine-methylene blue stain. × 125.

FIG. 4. Case 4. Alveoli show edema and an exudate of large mononuclear cells. Phloxine-methylene blue stain. × 125.

3



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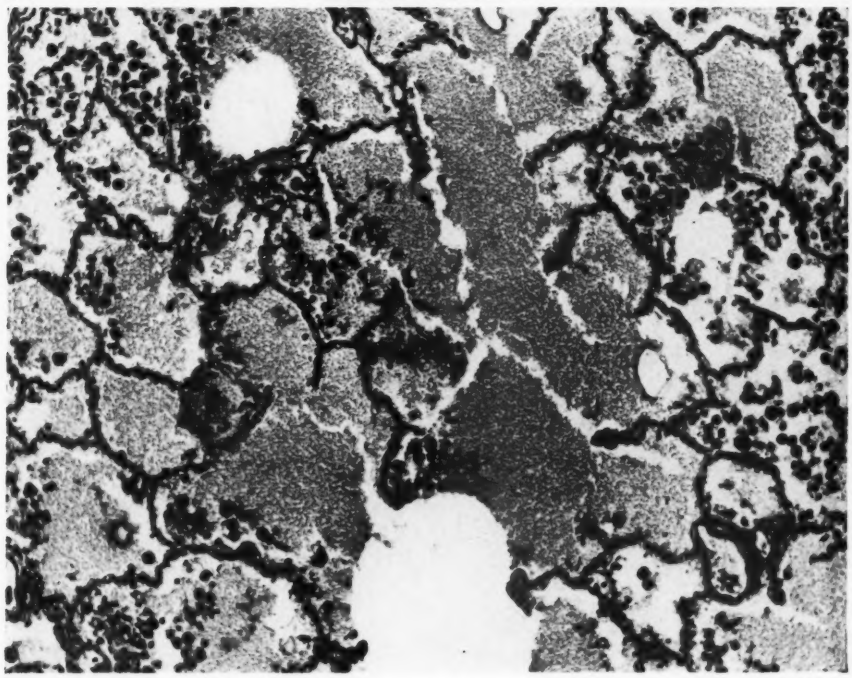

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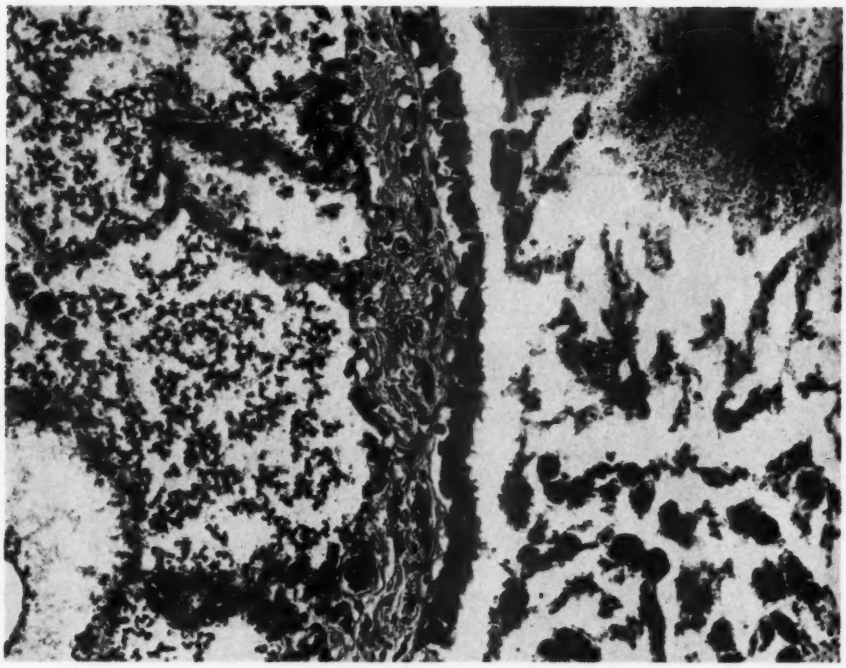
PLATE 155

FIG. 5. Case 5. Right upper lobe. Epithelium of bronchiole is intact. Lumen contains mucus and large mononuclear cells. Alveoli show edema. Phloxine-methylene blue stain. × 150.

FIG. 6. Case 1. Necrotizing tracheitis. Phloxine-methylene blue stain. × 80.

5



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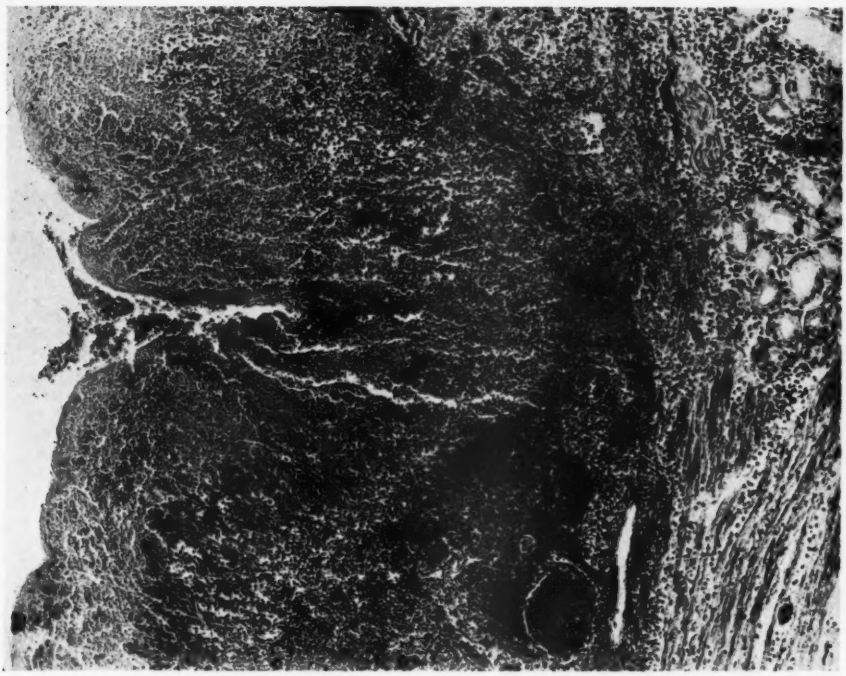

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THE SIGNIFICANCE OF HYPEREMIA AROUND TUMOR IMPLANTS *

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While using transplantable tumors in mice it was noticed that intense hyperemia develops around the tumor implants. An area of redness appears around the fragment of tumor within 18 hours after implantation, presumably before the amount of blood could be much increased by formation of new vessels.

A survey revealed a rather extensive literature upon vascular proliferation [1-5] in tumors, but an explanation of the hyperemia was not found. As the survival of a tumor in its host must depend in great part upon the establishment of an adequate blood supply, it is important to understand the mechanisms by which this is accomplished. Since local hyperemia is the first visible effect of the tumor upon the vessels of the host, preceding the formation of more intimate relationships between the host's vessels and the tumor, the significance of the hyperemia should be determined. It was for this purpose that the following experiments were done.

GROSS AND MICROSCOPIC OBSERVATIONS OF THE HYPEREMIC RESPONSE

When a fragment of transplantable tumor is implanted subcutaneously in the flank of a mouse it becomes surrounded within 18 hours by a pink blush. This soon develops into a deep red zone, 1 to 3 mm. wide, around the tumor. Engorged tiny vessels form tortuous channels, interlacing to make dense meshworks in the vicinity. The vascular engorgement extends eventually to the large vessels issuing from the axilla and groin. By the third or fourth day the hyperemia is extremely intense, and, when the skin is reflected to reveal it, is so conspicuous as to be apparent to an observer several yards away. The hyperemia persists until the tumor kills the mouse.

Microscopically, dilatation of capillaries to form large channels is apparent (Fig. 1). The vessels dilate until by the third day they measure 3 or 4 times the diameter of normal vessels. These vascular changes in the tissues adjacent to the implanted tumor are apparent before the ingrowth of vessels into the tumor, or the envelopment of vessels by it.

I. Failure of Homologous Adult Muscle Tissue to Excite Local Hyperemia

The first question we attempted to answer was, does the hyperemia around the tumor implants depend only upon the presence of foreign

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tissue? Would any piece of tissue, for example, homologous adult muscle implanted subcutaneously, cause local hyperemia?

Fresh muscle tissue from the thigh of an adult C57 mouse was implanted subcutaneously in the right flanks of 18 mice of the same strain. Into the left flanks of these mice was implanted Tumor 241* (this tumor is a fibrosarcoma, Fig. 2, induced several years ago with dibenzanthracene and since maintained by serial transfer in this strain of mice, in which it "takes" 100 per cent). Individual mice were sacrificed from 27 hours to 8 days after implantation of the tissues, and the local vascular reaction on the two sides was compared.

Intense hyperemia was excited by Tumor 241 within 27 hours, and the hyperemia increased during the following days as the tumor grew larger. In contrast, no grossly perceptible changes were apparent in the vessels surrounding the implanted muscle fragments in any of the animals at any time (Fig. 3). The tumor implants consistently increased in size, while the pieces of muscle tissue gradually decreased in size, becoming barely perceptible by the eighth day.

From this experiment it appeared unlikely that the hyperemia resulted from the presence of foreign tissue as such.

II. Failure of Heterologous Tumor Tissue to Excite Hyperemia

Could this hyperemia depend upon the *neoplastic* character of the implants? If so, any neoplastic tissue should cause this local vascular response, for example, a tumor from an alien species.

Fragments of a transplantable rat tumor† were implanted in one flank of 24 C57 mice, while mouse Tumor 241 was implanted in the other flank. Individual mice were sacrificed from 2 to 10 days after implantation, and the state of the local vascular system around the implants was observed. Tumor 241 excited the characteristic vascular response, whereas the rat tumor caused no perceptible hyperemia in any of the animals. Tumor 241 grew progressively during the 10-day period, while the rat tumor steadily regressed.

This result makes it unlikely that the hyperemia depended upon the neoplastic character of the tissue.

III. The Induction of Local Hyperemia by Homologous Embryonic Tissue

Since the hyperemia did not appear to depend upon the presence of foreign tissue, nor upon the neoplastic character of the tissue, could it de-

* The mouse tumors used in this investigation were obtained from Dr. Margaret R. Lewis, Wistar Institute, Philadelphia.

† Tumor 303, a transplantable fibrosarcoma of the rat originally induced by methylcholanthrene, obtained from Dr. E. H. Yeakel, Wistar Institute, Philadelphia.

pend upon the presence of proliferating cells? In both of the preceding experiments the test implants (adult homologous muscle and heterologous tumor) failed to grow. Would tissue, other than neoplastic tissue, which grew cause hyperemia? For example, would homologous embryonic tissue excite the hyperemia?

Embryos were removed from a mouse nearing completion of gestation. Pieces of tissue were taken from the thighs of the embryos and implanted in the flanks of 25 adult mice of the same strain. Individual mice were sacrificed and examined from 2 to 12 days thereafter. Pronounced hyperemia surrounded the embryonic tissue. This hyperemia was fully as strong (Fig. 4) as when neoplastic tissue was implanted in a susceptible mouse. The hyperemia persisted as long as the embryonic tissue continued to proliferate. Usually by the 14th day the embryonic tissue was regressing, and as regression took place the hyperemia faded.

The result of this experiment was in accord with the hypothesis that the hyperemia was dependent upon cellular proliferation.

IV. Further Test of Dependence of Hyperemia on Proliferating Cells

However, it was possible to devise a more nearly crucial experiment by taking advantage of the following fact:

Mouse Tumor 1, an induced fibrosarcoma that "takes" 100 per cent in Bagg albino mice, when implanted in C57 mice grows for a few days and then regresses, leaving the mice resistant to subsequent implants of this tumor.[6] If the hyperemia depended upon the presence of proliferating cells, Tumor 1 in C57 mice should produce hyperemia upon the first implantation during the short period of growth of the implants. But the same tumor in the same mice should fail to excite hyperemia in subsequent implantations, when growth would not occur because of the resistance induced by the first implants.

Pieces of Tumor 1 were implanted in the flanks of 36 C57 mice. The tumors grew slowly for a few days. Mice sacrificed and examined during the first 3 days showed strong hyperemia surrounding the tumor fragments. By the fourth day, however, the hyperemia began to fade and the tumors were regressing. Eight days after the original implantation no observable tumors were present. At this time fresh fragments of Tumor 1 were implanted in the remaining mice, and individual mice were sacrificed and examined from the third to the twelfth day thereafter. No hyperemia was seen surrounding the new implants of tumor (Fig. 5) and the tumor fragments steadily regressed.*

Thus, the same tissue in the same mice gave different reactions de-

* Similar observations, although as yet unpublished, were made previously by Dr. Margaret R. Lewis.

pending upon whether or not the tissue grew. This result strongly supported the concept that the hyperemia surrounding these implanted tumors was dependent upon the presence of proliferating cells.

V. Failure of Artificial Hyperemia to Affect Resistance to Tumor Implants

Since hyperemia and cellular proliferation appeared so closely interrelated, it was suggested that artificially induced hyperemia might cause a tumor to grow in a resistant host, where normally its presence would not lead to hyperemia.

To test this hypothesis advantage was taken of the fact that tumor implants grow well when placed within subcutaneous pockets in the ear of the mouse (Fig. 6). The mouse ear is also a convenient place to create hyperemia, and, further, it is possible to use one ear as a control upon the other. The pinna of the mouse is thin and the blood vessels can be observed directly both grossly and microscopically [7] in the living animal.

Fifteen C57 mice were made resistant to Tumor 1 by implanting it in their flanks and allowing it eventually to regress. When regression was complete, as judged by the absence of visible or palpable tumor, the left pinna of each mouse was irradiated with ultraviolet light, sufficient to produce hyperemia (6 to 7 minutes at 12 inches using a UVIARC lamp). After this irradiation, tiny pieces of Tumor 1 were implanted in both the left (irradiated) and right (nonirradiated) ears. The nonirradiated ear thus served as a control on the tumor resistance in each animal. The hyperemia in the left ear appeared on the day after irradiation and persisted for about a week, during which time the tumors were observed. No growth occurred in either ear of any animal. Thus the attempt to overcome the induced tumor resistance by artificially exciting local hyperemia around the tumor implants was unsuccessful.

From this experiment it is concluded that the failure of growth of tumor in a tumor-resistant animal depends upon other factors than the absence of hyperemia.

Hyperemia develops because the tumor grows, not vice versa.

Discussion

The first visible effect of an implanted tumor upon the blood vessels of the host is local hyperemia. This hyperemia precedes the growth of new vessels into the tumor, or the envelopment of vessels by growth of the tumor. The experiments reported in this paper indicate that the hyperemia is excited not by neoplastic tissue as such, but by the presence of proliferating cells. This suggests the early establishment of a

reciprocal relationship between the tumor and the local vascular system of the host. If the tumor cells proliferate, hyperemia is excited, increasing the flow of blood to the part. The increased flux of blood would presumably operate advantageously to the mass of actively dividing cells. Hyperemia is the first apparent step in the process whereby the host's vessels and the growing tumor become intimately associated. Whether vascular proliferation is aided by, or dependent upon, a preceding hyperemia has not been determined.

Summary and Conclusions

Intense local hyperemia is a constant finding in the vicinity of transplantable mouse tumors. Experiments were directed toward determining the significance of this phenomenon.

It was found that hyperemia appeared within 18 hours after implantation and was progressive thereafter so long as the tumor grew.

Implants of homologous adult muscle tissue failed to produce hyperemia, indicating that hyperemia was not caused merely by the presence of foreign tissue.

Heterologous tumor implants did not produce hyperemia, showing that the vascular response did not depend upon the fact that the tissue was neoplastic.

Homologous embryonic tissue, which grew for a time in the host, excited strong hyperemia that faded as the embryonic tissue finally regressed. This suggested that the hyperemia was due to the presence of proliferating cells.

Tumor 1, from Bagg albino mice, when implanted in C57 mice grows for a time and then regresses, leaving the mice resistant to subsequent implants of this tumor. It was found that the initial implants of Tumor 1, during their short growth period, produced hyperemia, whereas subsequent implants of the same tumor in the same mice did not grow and did not cause hyperemia.

It is concluded from the several experiments that the hyperemia around transplanted mouse tumors is due to the presence of proliferating cells.

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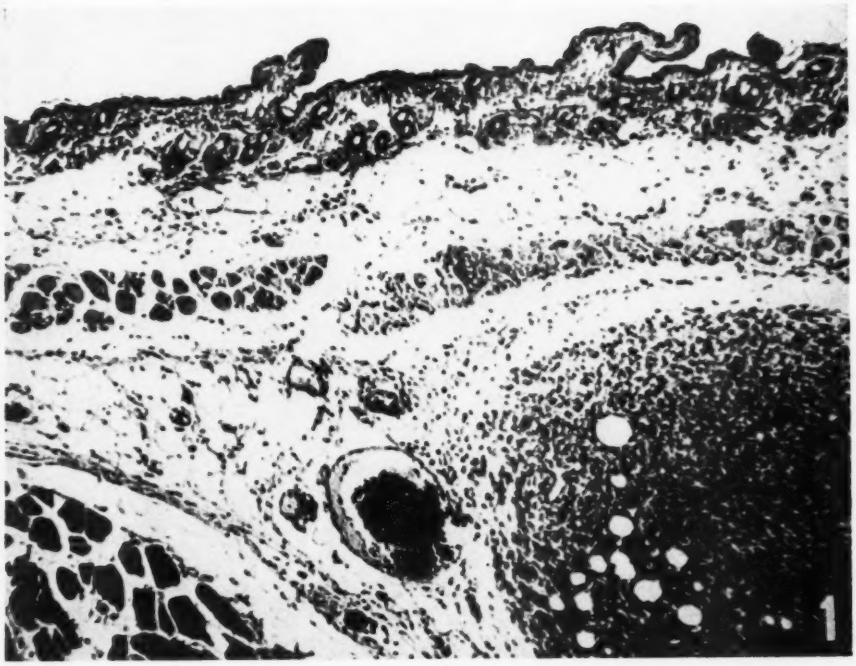
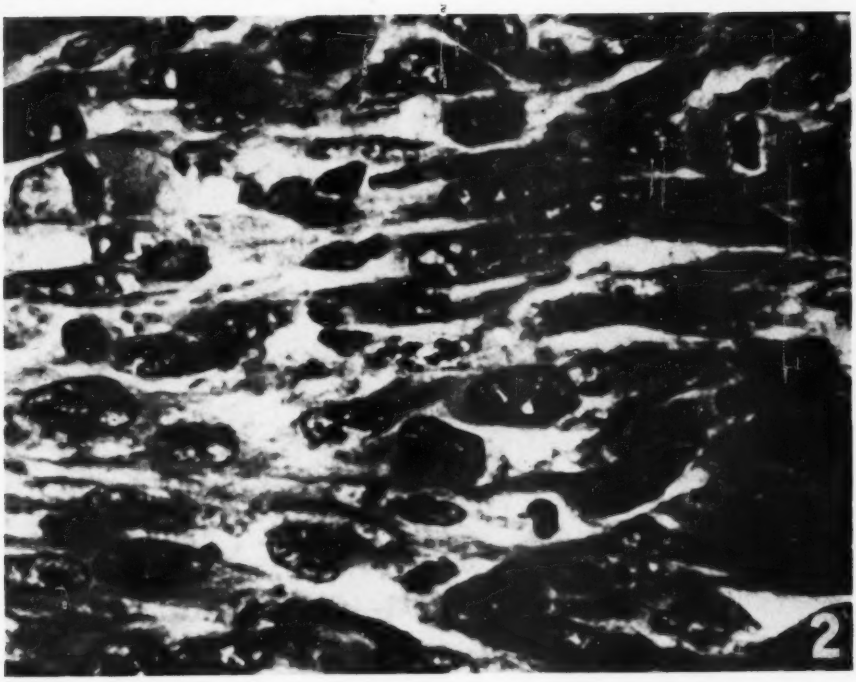
DESCRIPTION OF PLATES

PLATE 156

FIG. 1. Low-power photomicrograph of a transplantable mouse tumor 5 days after subcutaneous implantation. The tumor is in the right lower corner. Several large blood vessels are seen at the edge of the growing tumor. × 110.

FIG. 2. High-power photomicrograph of a transplantable mouse tumor (Tumor 241) used in the experiments described in this paper. Structure is that of a fibrosarcoma. × 970.



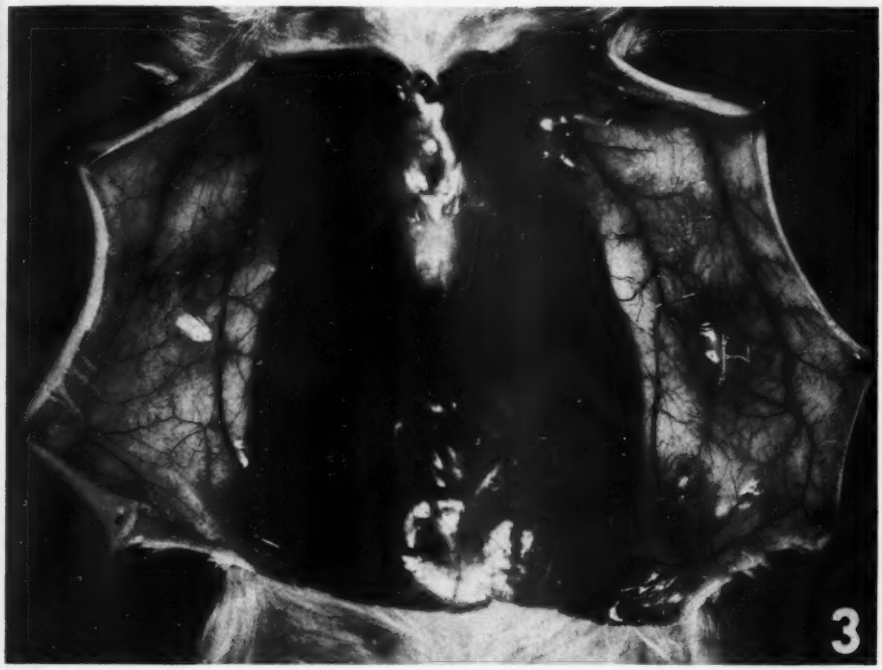


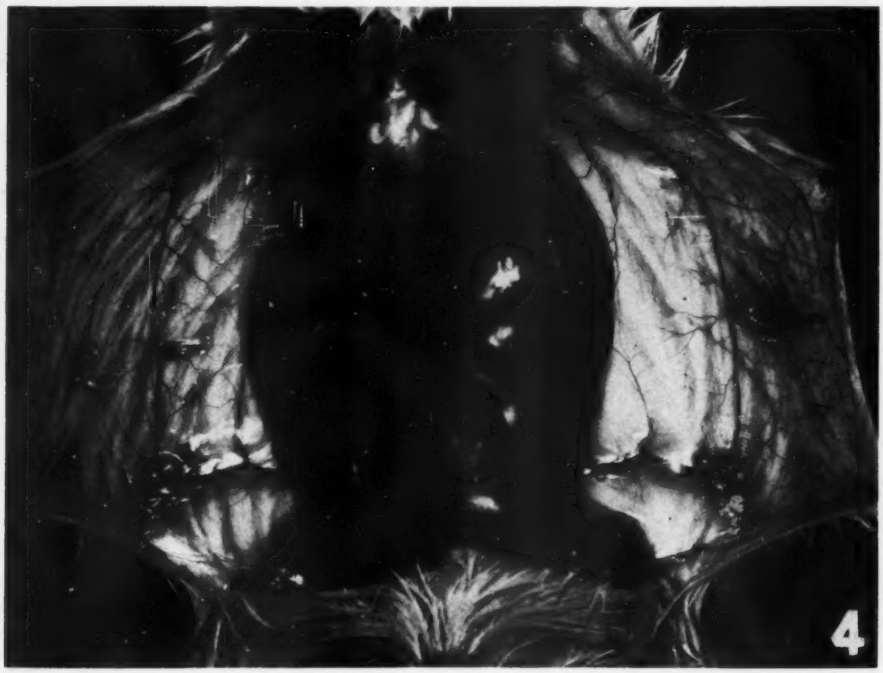
Coman and Sheldon Hyperemia Around Tumor Implants

PLATE 157

FIG. 3. A mouse, with the skin reflected to expose subcutaneous implants and vessels in flanks. The fragment on the right (in the photograph) is transplantable tumor, 3 days after implantation. Of note are the intense hyperemia and the dilatation of even the large vessels. The fragment on the left is homologous muscle tissue. Hyperemia is not present around the muscle.

FIG. 4. Implants of homologous embryonic tissue in the right (in the photograph), and homologous adult muscle in the left, flanks of a mouse, 5 days after implantation. The embryonic tissue has excited a strong local hyperemia. No hyperemia surrounds the fragment of adult muscle tissue, which is barely discernible just medial to the largest vessel, near its mid-point.



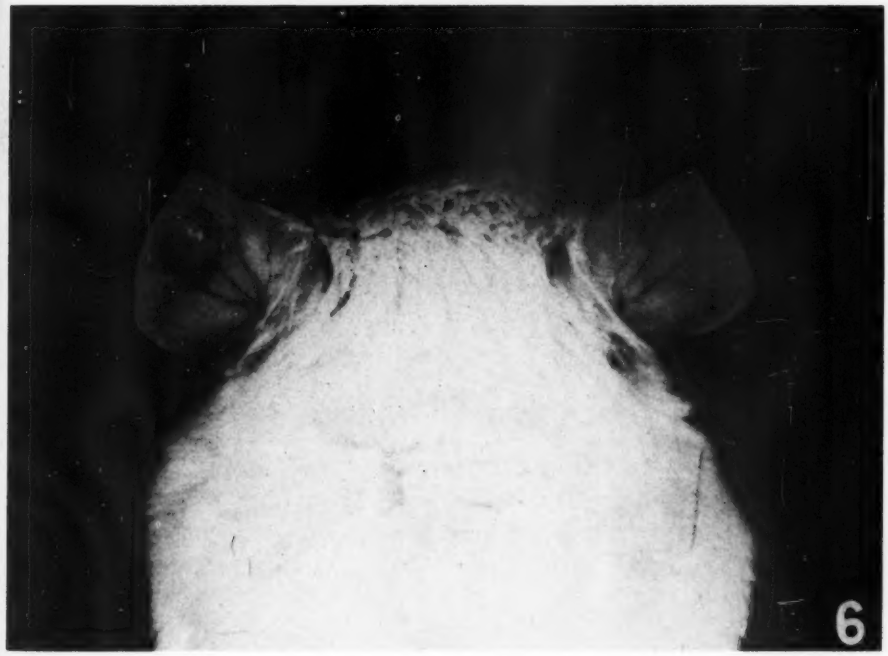


Coman and Sheldon Hyperemia Around Tumor Implants

PLATE 158

FIG. 5. Tumor implants in resistant host. A C57 mouse in which a fragment of Tumor I (from a Bagg albino mouse) was previously allowed to grow and regress, thus establishing resistance to further implants of Tumor I. Subsequently Tumor I was implanted (pale linear mass, right side of photograph) and failed to excite hyperemia. In contrast, Tumor 241, to which the animal was susceptible, excited intense local hyperemia as seen on the left. The implants are of 3 days' duration.

FIG. 6. Photograph of mouse showing use of the pinna as a site of tumor implantation. The vessels are widely dilated in the tumor-bearing ear.



Coman and Sheldon Hyperemia Around Tumor Implants

MEDIASTINAL CHORIONEPITHELIOMA IN A MALE

A Case Report *

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The knowledge that chorionepitheliomas in females originate in the epithelium of the chorionic villi was first established by Marchand [1] in 1895, at which time he carefully elaborated and clarified the histology of this tumor. It was not until 1902 that Schlagenhaufer,[2] among others, described the development of this tumor in males from chorionepithelium arising from germinal cells of the testis or teratomatous tissue. Since that time, despite the many reports of chorionepitheliomas of genital origin in males, very few extratesticular tumors of this type have been reported. Moreover, the lack of adequate criteria for the establishment of the extragenital origin of these neoplasms has caused considerable controversy among the writers on this subject as to just which cases may be considered sufficiently well documented to be accepted as extragenital tumors. Heaney,[3] Kantrowitz,[4] Erdmann, Brown, and Shaw,[5] and others have each published collected series in which the cases accepted differ from author to author.

Much of the confusion has arisen from the fact that tumors primary in the testes may not only be extremely small, but moreover may spontaneously regress and "heal," leaving microscopic scarring as the only permanent vestige of the former neoplasm (Prym,[6] Craver and Stewart [7]). Therefore, before a case can be definitely accepted as of extragenital origin, the testes must be ruled out as the primary site. Cases in which markedly atrophic testes have been found, or in which no microscopic examination of the genitalia was done, must be excluded. Whether serial sections of the genitalia must be examined in all cases, as suggested by Prym and by Erdmann, Brown, and Shaw, would seem to depend largely upon the individual case, and we agree with Frank [8] that a distinct mediastinal teratoma is a reasonable site of origin for a mediastinal chorionepithelioma when the testes have been carefully studied by multiple sections and found to be negative, even if not by serial sections.

On the basis of these criteria, 14 cases may be listed as established extragenital chorionepitheliomas in males, reported to date (Table I).

The purpose of this report is to present an additional case, primary in the mediastinum, occurring in a 26-year-old male who entered the Boston City Hospital in 1935 and was autopsied at the Mallory In-

* Received for publication, September 20, 1945.
† Now on leave of absence with the U. S. Navy.

stitute of Pathology in the same year. The extragenital origin of this tumor has been adequately established by careful examination of the testes, which were not only grossly negative on serial section but were likewise free of neoplasm in the thirty-two representative blocks of the testes studied microscopically.

While no distinct, well differentiated teratoma could be identified within the mediastinal tumor, the considerable size of the tumor (10 by 9 by 8 cm.) made serial microscopic sections of the mass impractical. However, the identification of two distinct histologic types of tumor within the thoracic growth, namely, chorionepithelioma and embryonal carcinoma, makes the teratomatous origin of this mixed neoplasm seem likely.

TABLE I

Reported Cases of Extragenital Chorionepitheliomas in Males

Case	Author	Date	Age	Primary site
1	Miller and Browne[9]	1922	39	"Posterior to liver"
2	Krasnjanskaja[10]	1930	72	Undetermined, "not in testes"?
3	Arendt[11]	1931	20	Mediastinum
4	Heaney[3]	1933	40	Retroperitoneal
5	Kantrowitz[4]	1934	22	Anterior mediastinum
6	Fenster[12]	1934	27	Retroperitoneal
7	Gerber[13]	1935	23	Retroperitoneal
8	Weinberg[14]	1939	70	Bladder
9	Mathieu and Robertson[15]	1939	27	Retroperitoneal
10	Erdmann, Brown, and Shaw[5]	1941	45	Retroperitoneal
11	Hyman and Leiter[16]	1943	57	Bladder
12	Plenge[17]	1944	30	Retroperitoneal
13	Stowell, Sachs, and Russell[18]	1945	15	Intracranial
14	Laipply and Shipley[19]	1945	13	Mediastinal

REPORT OF CASE

E. C. H., a 26-year-old elevator operator, was admitted to the Boston City Hospital on March 28, 1935, complaining of pain in the right chest. He had been perfectly well until 3 weeks before, at which time he had experienced a heavy feeling under the sternum while at work. He also began at that time to feel weak and to lose his appetite. The chest symptoms soon developed into sharp, knife-like pain radiating from the sternum over the right upper chest towards the shoulder, and also from the region of the right nipple over the shoulder and down to the right mid-back. A cough appeared which was at first productive of brownish yellow sputum, which later was tinged with bright red blood. The pain soon became severe enough to interfere with his sleep, causing him to sit up in bed in a vain effort to gain relief. Coughing or deep breathing aggravated the pain, and approximately 1 week after the onset of his first symptoms he noted marked shortness of breath both on exertion and at rest. He had five or six attacks of epistaxis. Later he began to feel nauseated and vomited twice. The vomitus was not bloody. He stopped work the day before admission because of the pain and the increasing dyspnea, weakness, and dizziness. He stated that he believed he had lost 18 pounds during the 2 months preceding admission.

The past history and family history were irrelevant.

Physical Examination. The patient was a well developed and well nourished adult male who was lying in bed and appeared ill and uncomfortable. His voice sounds were normal but he talked in paroxysms due to the dyspnea created by the effort of talking.

The eyes, ears, nose, and throat were normal.

The neck showed distention of the superficial veins with marked tortuosity. A tracheal tug was palpable above the manubrium. The thorax appeared slightly asymmetrical with a suggestive prominence of the right chest, which appeared to move less than the left on respiration. Both breasts were more prominent than is normal, with deep, circular, firm areas about 4 to 5 cm. in diameter under each nipple. These masses were freely movable and nontender. There was dullness to flatness over the upper right lung field and breath sounds were absent in this area. The lung base on this side was high and there was hyperresonance over the right lower chest. The left lung and the heart were within normal limits.

The external genitalia were normally developed. Both testes were regular, equal in size, and of normal elasticity.

Axillary and inguinal lymph nodes were bilaterally palpable but not markedly enlarged.

The remainder of the physical examination was negative.

Laboratory examinations revealed the following: red blood cell count, 4,400,000 cells per cmm.; hemoglobin, 74 per cent; white blood cell count, 6,500 cells per cmm.; differential, normal except for 5 per cent eosinophils. The urine contained no albumin, sugar, or abnormal sediment.

Clinical Diagnoses. Occlusion of the superior vena cava; right hydrothorax; gynecomastia; lymphosarcoma of mediastinum; question of teratoma of mediastinum.

Clinical Course. The patient went progressively downhill with rapidly increasing dyspnea and cyanosis. The cough became more severe and hemoptysis more marked. On the eleventh day of his hospital stay death occurred suddenly without premonitory signs or symptoms.

POST-MORTEM EXAMINATION

Autopsy was performed 12 hours after death. The body was that of a well developed and well nourished, young adult male. Both breasts were hypertrophied and firm. Cross section revealed each to be composed of a circular, flat mass of white, firm tissue, 4 cm. in diameter and 2.5 cm. thick, centered under the nipple.

The peritoneal cavity was without pathologic change.

The pleural cavity on the right contained 900 cc. of dark red, cloudy fluid. The left cavity contained approximately 100 cc. of similar fluid. There was a large, moderately firm, friable, dark red mass with yellow-white and tan areas in it, measuring 10 by 9 by 8 cm., in the superior portion of the mediastinum. It was attached firmly to the upper lobe of the right lung medially and to the anteromedian surface of the left upper lobe by a few fibrous adhesions. The anterior portion of the great vessels and trachea and bronchi were embedded in the mass which on section proved to be friable, spongy, red-brown tissue similar to that described above. Postero-inferiorly the neoplastic tissue ap-

peared firmer and yellow-white. Invasion of the anterior wall of the superior vena cava at the junction of the left and right innominate veins by neoplastic tissue had occurred with the production of almost complete occlusion of the superior vena cava. The tumor caused a marked compression of the main portion of the azygos vein, as well as marked compression with almost complete occlusion of the branches of the right bronchus entering the upper and middle lobes. A friable, red, spongy mass, in which there were large areas of blood clot, replaced the normal structure of the right upper lobe and upper half of the middle lobe. This mass was slightly larger than the mediastinal tumor and was fimly fixed to the parietal pleura by fibrous adhesions.

The pericardial cavity contained 100 cc. of blood-tinged fluid. A friable, red tumor nodule extended through the anterosuperior portion of the parietal pericardium and protruded into the pericardial sac for 2 to 6 mm. over an area 3 by 1 cm. The tumor nodule was not adherent to the epicardium. The heart weighed 340 gm. and was entirely within normal limits.

The left lung weighed 750 gm. The right was not weighed. In the right upper lobe and upper half of the middle lobe was found the mass previously described. The cut surface of the tissue exactly resembled the tumor previously described, and serial sections of the mass showed it to be continuous with the tumor in the mediastinum. The remainder of the middle lobe and the lower lobe were flabby, collapsed, and subcrepitant with many round metastatic nodules, varying from 0.5 to 3.5 cm. in diameter, scattered throughout. The left lung contained nodules similar both in size and character, scattered throughout a gray-red, crepitant parenchyma.

The liver weighed 2230 gm. In the anterosuperior portion of the right lobe there was an irregularly spherical mass of friable, spongy, dark red tumor, 8 cm. in diameter, similar to that found in the lung and mediastinum. This had extended through the capsule and was attached to the surface of the right dome of the diaphragm. The remainder of the liver was brown-red and was of the usual consistency.

The brain weighed 1440 gm. There was a moderate generalized flattening of the convolutions. A mass of obvious neoplastic tissue, 2 cm. in diameter, was found in the right cerebellar hemisphere involving the medio-inferior portion of the dentate nucleus and bulging into the fourth ventricle. The pituitary gland was grossly negative.

The remainder of the post-mortem examination was negative with particular attention having been devoted to the genital organs (penis, prostate, seminal vesicles, and testes).

Microscopic Examination

The only histologic features of interest in addition to the tumor were found in the breasts, pituitary gland, and testes. In the soft, hemorrhagic areas the mediastinal tumor presented the typical microscopic picture of a chorionepithelioma with masses of anaplastic syncytium-like cells in a bloody matrix (Fig. 1). The cells were characteristically extremely pleomorphic, with acidophilic cytoplasm, and sometimes with indistinct cell boundaries forming syncytium-like masses. Mitotic figures were numerous. In contrast, sections from the more solid, white areas of the tumor showed a uniform growth of large, round, undifferentiated tumor cells with little cytoplasm and regular, round nuclei having finely divided chromatin and widely scattered mitotic figures (Fig. 2). Careful search for well differentiated, teratomatous tissue was unsuccessful. However, as was previously stated, the occurrence of two distinct histologic types of neoplasm within a single tumor mass strongly suggested the differentiation of a teratoma into two related neoplasms.

The breasts showed fairly generalized cellular hyperplasia with proliferation of the duct epithelium so that the cells were heaped upon one another, creating a lining two or three cells thick (Fig. 3). There was scattered rudimentary gland production, but no evidence of secretory vacuolization of the epithelial cells could be found.

Careful microscopic search of thirty-two sections of testes and other sections of epididymides and spermatic cords failed to disclose evidence of neoplasia or residual scarring.

The tubular epithelium showed good spermatogenesis with occasional atrophic, slightly fibrosed tubules. There was a slight focal increase in the number of interstitial cells.

The pituitary body was quite remarkable. In addition to oxyphilic, chromophobic, and basophilic cells, other cells were present. The cytoplasm of these cells in hematoxylin and eosin stains was red, but not as strikingly red as the cytoplasm of the eosinophilic cells, and their contours were not distinct. These cells constituted a considerable proportion of the anterior lobe, giving the impression of hyperplasia (Fig. 4). Many mitotic figures were found.

Anatomic Diagnoses. (1) Chorionepithelioma and embryonal carcinoma, primary in the mediastinum and probably of teratomatous origin, with direct extension into the right lung, pericardium, and superior vena cava; (2) subtotal occlusion of the superior vena cava; (3) metastasis to both lungs, liver, and right cerebellar hemisphere; (4) compression of the azygos vein and main bronchi to the upper

and middle lobes of the right lung; (5) gynecomastia; (6) changes in the pituitary body consistent with pregnancy.

Many hormone assays were performed in this case, one on the urine prior to death and several on the urine and various tissues obtained at autopsy. The results are tabulated in Table II.

Discussion

The question whether this mediastinal tumor arose directly from aberrant sex cells in the mediastinum or through the development of a teratoma is largely academic and, for reasons previously stated, must remain in this case unanswered. According to Ewing,[20] these sex cells may occur anywhere along the entire length of the embryonal entoderm

Table II

Hormone Assays

Source	Follicle-stimulating hormone	Luteinizing hormone	Estrogens
	(*rat units*)	(*rat units*)	(*castrate mouse units*)
Urine, 1 week prior to death	330,000*	50,000*	783*
Urine, autopsy	1,300,000*	330,000*	
Tumor, 1 kg. of wet tissue	1,040,000†	260,000†	60–430†
Breast, 1 kg. of wet tissue	330,000†	26,000†	less than 50†

* Units per liter.
† Units per kg. of wet tissue.

and may thus be found within the mediastinum. However, most authors agree with Kaufmann [21] that true extragenital chorionepithelioma probably always arises in teratomatous tissue.

The case reported here presents a fairly typical clinical picture of mediastinal chorionepithelioma. The age of our patient was 26 years, which is 10 years less than the average age at death of the tabulated cases. Hörnicke [22] collected 35 cases of chorionepithelioma in males in which the age had been mentioned and 23 of the patients were between 20 to 40 years of age at death. We, too, have found that of 26 cases mentioned or reviewed in this paper, all were between 20 to 40 years of age except 6 (13, 15, 45, 57, 70, and 72 years, respectively).

The symptoms presented by our patient were characteristic of this type of mediastinal lesion, with pain referred to the anterior mid-chest and right nipple region, radiating to the shoulder and back. The intensification of the pain on coughing is common to many. The dyspnea, orthopnea, cough, bloody sputum, and weight loss presented by this

patient are likewise frequently seen in these cases. On occasion, cerebral symptoms are encountered, usually due to metastases.

Gynecomastia is a common finding and is so characteristic as to suggest the diagnosis in certain instances. The chorionic tissue in the tumor functions in a fashion analogous to a pregnancy with the production of (1) follicle-stimulating and luteinizing hormones that can be demonstrated in the urine and blood, (2) changes in the pituitary glands resembling those of pregnancy, and (3) breast changes. In eight instances in the literature colostrum formation was noted in these cases of gynecomastia. This finding is not common, however, and the absence of colostrum formation in this case, as well as the rarity of its

TABLE III

Time Relationships of the Breast Changes Associated with Chorionepithelioma in Males

Authors	Age	Duration	Breasts
Entwisle and Hepp[23]	22 years	5 months	Gynecomastia with colostrum
Friedländer and Moses[24]	38 years	6 months	Gynecomastia with colostrum
Melicow[25]	20 years	7 months	Gynecomastia
Jüngling[26]	27 years	6 months	Gynecomastia
Bonn and Evans[27]	34 years	5 months	Gynecomastia
Gilbert[28]	25 years	3 months	Gynecomastia and microscopic colostrum
MacDonald[29]	40 years	3 months	Gynecomastia
Kirwin[30]	34 years	11 weeks	No gynecomastia
Jüngling[26]	26 years	8½ weeks	Gynecomastia not mentioned clinically, found histologically
Fortner and Owen, quoted by Mathieu and Robertson[15]	38 years	2 months	Marked hypertrophy
	40 years	1 month	Slight hypertrophy

occurrence in previously described cases, is probably due to the fact that the undeveloped male breast requires a longer time to develop glandular hyperplasia and secretory activity than does the female breast. Our patient died 1 month after the onset of his clinical symptoms and probably there was insufficient time to permit the development of significant glandular secretory activity.

Analysis of the cases in the literature in which the condition of the breasts was mentioned (Table III) would seem to indicate that at least 3 months must elapse before colostrum formation can be reasonably anticipated, and even then its occurrence is not invariable.

The widespread assumption that gynecomastia is preceded by atrophy or destruction of testicular tissue would appear to be disproved by this case of extragenital chorionepithelioma as well as by many reported cases, in all of which intact testes were found.

The development of so-called "pregnancy cells" in the pituitary

body has long stimulated observers to speculate as to their significance. Erdheim,[31] in 1936, expressed the hypothesis that the cells might be endocrinologically active, secreting a growth-promoting hormone. Cases in which chorionepithelioma have been found in children tend to support this view, such as the series reported by Sturley,[32] in 1942, of thirteen cases of ovarian chorionepithelioma in children up to the age of 13 years with the finding of precocious sexual development in all. According to Erdheim, many of the authors' preoccupation with the abnormal sexual development in children frequently led to their overlooking a markedly precocious bodily development. Fasold [33] and Siegmund,[34] both reporting well documented cases of chorionepithelioma in childhood, noted marked growth in height, disproportionate for their age, in children with these tumors, possibly associated with the pregnancy-like cells in the pituitary body.

Ever since the time of Meyer [35] and Aschheim and Zondek,[36] the Aschheim-Zondek test has been used to detect chorionepithelioma in females. Heidrich, Fels, and Mathias [37] made the analogous observation in males, and the test has since been used in males and females not only to confirm the diagnosis, where suspected, but also to detect recurrence or metastases of the tumor postoperatively by demonstrating in the urine hormone titers in excess of the levels encountered in normal pregnancies, with progressively rising values as the tumor increases in size.

Summary and Conclusions

1. A case of a 26-year old male with a large chorionepithelioma primary in the mediastinum, presumably arising in a teratoma, is described.

2. Serial sections of both testes taken 2 mm. apart showed no gross or microscopic evidence of tumor.

3. Gynecomastia, a positive Aschheim-Zondek test, and changes in the pituitary body resembling those seen in pregnancy were all present.

4. Fourteen other cases of extragenital chorionepithelioma in males have been collected from the literature.

5. The greatest incidence of these lesions is found in the third and fourth decades of life.

6. Gynecomastia, or at least glandular hypertrophy, is frequently found in these cases in males, and in certain instances colostrum formation has been observed.

7. Inasmuch as a primary tumor in the testes may be extremely small or may regress to microscopic size, metastasis from the testes must be considered and ruled out in all instances of supposed primary

extragenital chorionepithelioma by a thorough examination of those organs, preferably by multiple sections examined microscopically.

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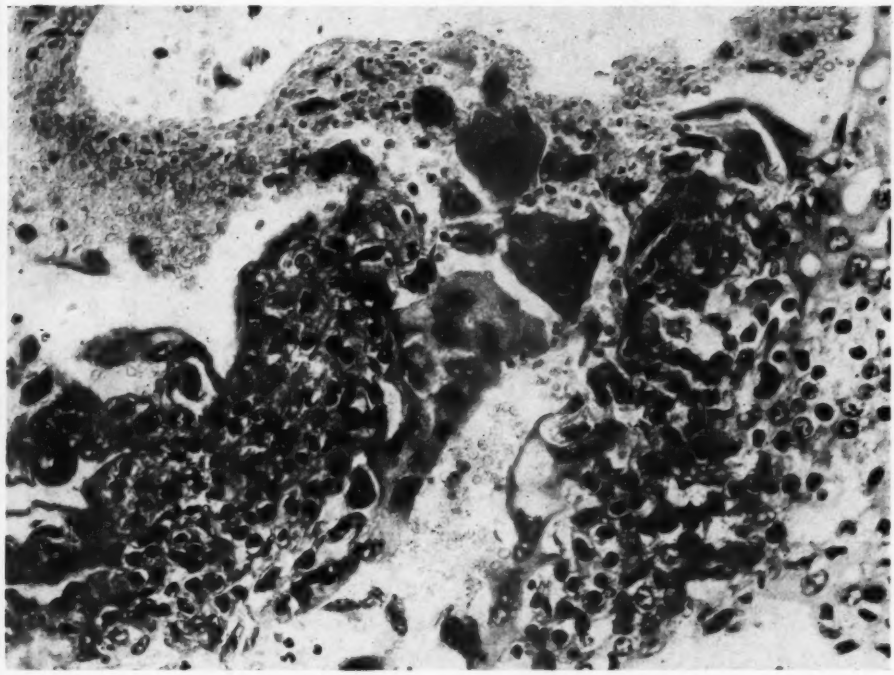
DESCRIPTION OF PLATES

PLATE 159

FIG. 1. Mediastinal tumor showing the two types of epithelium characteristic of chorionepithelioma. Phloxine-methylene blue stain. × 175.

FIG. 2. Mediastinal tumor. Undifferentiated portion growing as round to polygonal cells. Phloxine-methylene blue stain. × 265.

1



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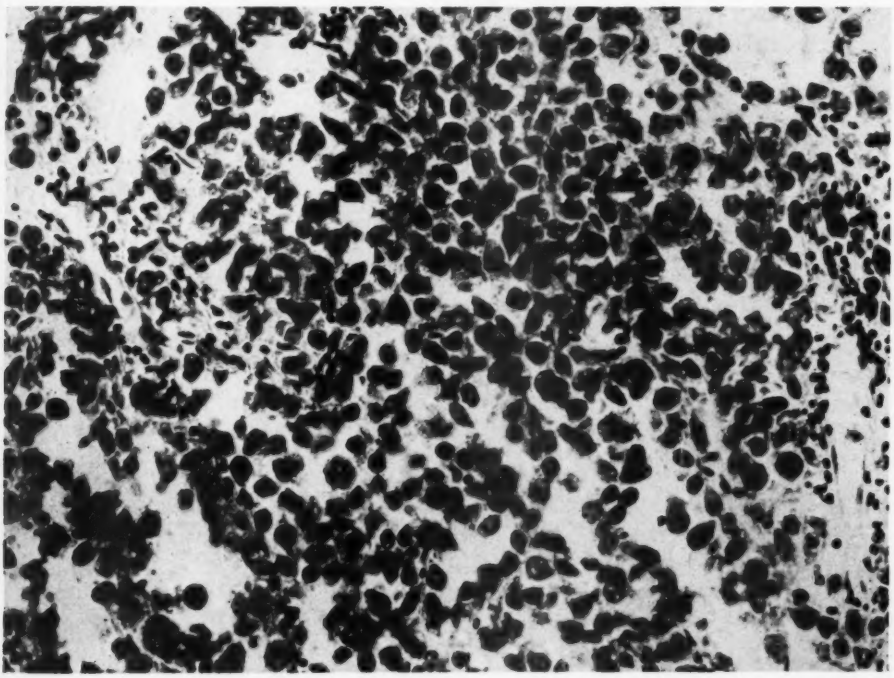


Hirsch, Robbins, and Houghton Mediastinal Chorionepithelioma in a Male

PLATE 160

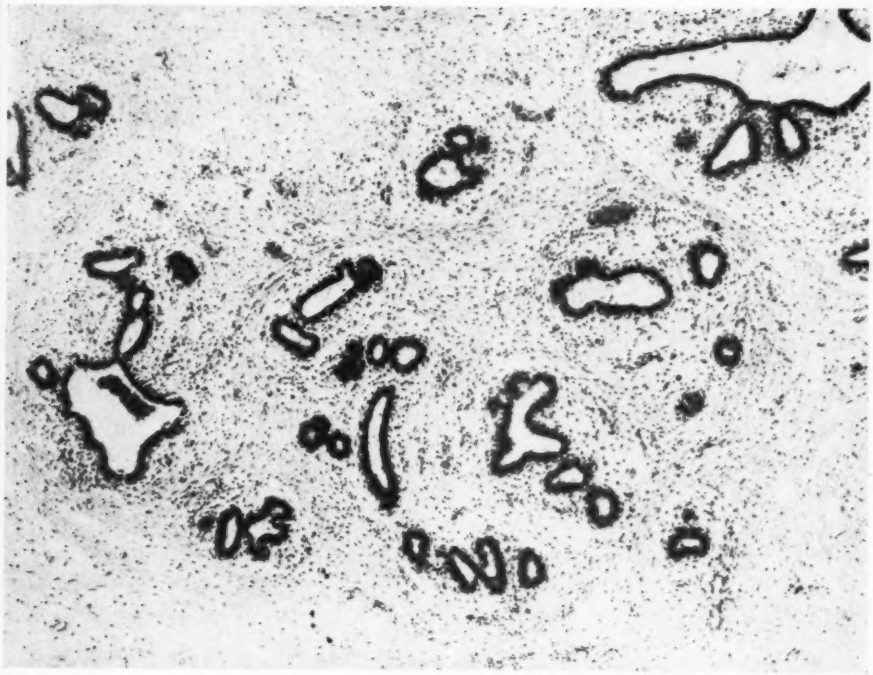
FIG. 3. Breast, showing histologic picture of gynecomastia. Phloxine-methylene blue stain. × 130.

FIG. 4. Pituitary body. The majority of the cells are the so-called pregnancy cells. Hematoxylin and eosin stain. × 575.

3

4

3



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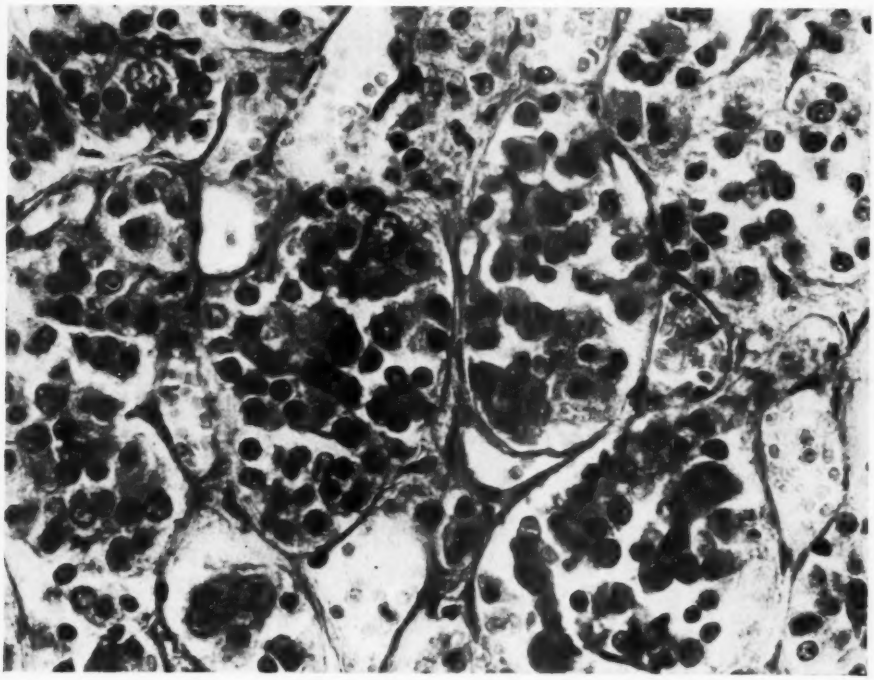

Hirsch, Robbins, and Houghton Mediastinal Chorionepithelioma in a Male

MEDIAL HYPERPLASIA IN PULMONARY ARTERIES OF CATS *

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In the course of pharmacologic investigation, one of us (W. M.) has examined microscopic sections from the lungs of more than 150 cats. In two of these there was advanced hypertrophy and hyperplasia of the smooth muscle of the intrapulmonary arteries, but there was nothing similar to this in the other cats examined. A third cat (no. 2), received from another source, showed the same change. We have found no reference to this lesion in cats except for notes by Ettinger [1, 2] on an apparently similar condition. In view of the rarity of this condition, the findings in these three cats will be described, with consideration of a number of controls.

Cat 1

An adult male cat of unknown age, that weighed 3.32 kg., died 5 minutes after injection of 120 mg. per kg. of silicic acid into a saphenous vein. An incomplete autopsy was performed, and no lesions were noted except in the lungs. The lungs showed the congestion frequently associated with this experimental procedure. When parts of the lungs were preserved in a 4 per cent solution of formaldehyde, gray nodules about 2 mm. across were seen, both around the bronchi and under the pleura.

Microscopically, there were smaller separate nodules and confluent groups of similar structure, both found to represent arteries with enormously thickened walls and very small or even apparently obliterated lumina (Figs. 1 and 2). The hypertrophy was limited to the media. The endothelium, subendothelial connective tissue, and peripheral connective tissue were intact. The internal elastic lamina was moderately wavy in many instances, but otherwise not unusual. The media was formed of a very thick layer of concentrically arranged, spindle-shaped cells, with the structure of large smooth muscle cells. They were purple with Masson's and with Mallory's connective tissue stains. All of the arteries in the sections showed the same change. The lesion was clearly a chronic process, entirely unrelated to the experimental procedure. Congestion of the intra-alveolar blood vessels was attributed to the intravenous congestion. The bronchi were normal except for narrowing due to pressure from the adjacent hypertrophic arteries.

The arteries present in the sections have been measured with a

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screw micrometer in the ocular of a microscope. In many cases the arteries were cut so obliquely that accurate measurement was impossible. In others, the vessels could be measured with reasonable accuracy. The wall of each vessel (W) was measured twice in the center of each quadrant, and these eight readings averaged. The lumina (L) were measured twice in each of two axes, perpendicular to one another, and these four readings averaged. The resulting ratios (W:L) are expressed in the same terms as were used for measuring human arterioles by Kernohan, Anderson, and Keith [3] and Morlock.[4] It should be noted that the average thickness of one wall is compared to the average diameter of the lumen. The external diameter of each artery would be represented by $2W + L$, not by $W + L$. The results have been plotted in Text-Figure 1, the ordinates indicating the external diameter of the vessels, the length of the horizontal lines denoting the ratio of the average thickness of the wall of each artery to the size of its lumen (W:L). In the ten vessels measured, the average of the ratio W:L was 1.36 (eight times that of the control animals).

Cat 2

A common male Maltese cat was castrated when 3 months old. He was a pampered pet of a pharmacy, where he apparently received more than ample portions of food. Several weeks before death he was treated for an abscess that followed the bite of another cat, but he made an apparently uneventful recovery in the Raritan Hospital for Animals. He died when 23½ years old.

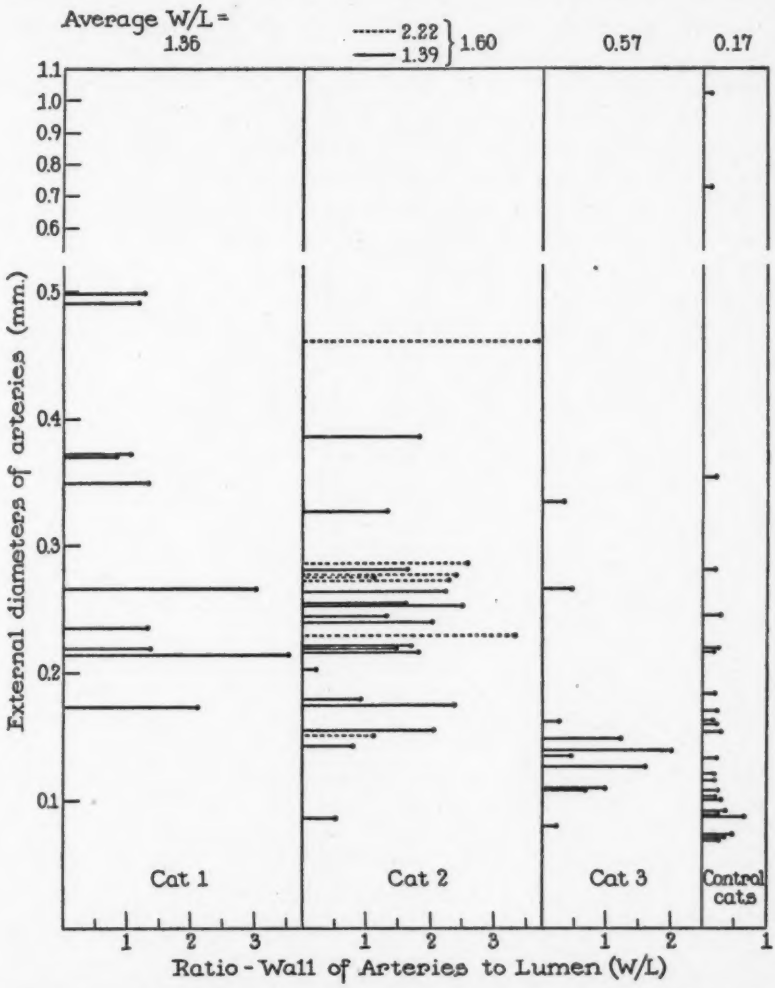
At autopsy (J. A. S.), the fur and teeth were in good condition. There were 50 cc. of green pus in the left pleural cavity, and the left lung was collapsed and covered with fibrinous exudate. There was some fibrin on the right pleural surface, but no evident pneumonia. On macroscopic section the bronchi of both lungs were prominent, and thickened arterial branches were recognized in all lobes.

On microscopic examination the left lung showed fibrinopurulent pleurisy, pulmonary abscess, acute bronchitis, and bronchopneumonia with early organization. The pleura overlying the right lung was covered by a little fibrin, but the parenchyma of this lung was almost completely expanded, and contained no exudate.

The arteries in the inflammatory and noninflammatory areas of the lungs showed a similar thickening of their walls. They were like those in cat 1, except that in this cat there was more connective tissue and smooth muscle inside the thick, circular layer of muscle. The average W:L ratio of the seven arteries in inflammatory tissue (indicated in Text-Fig. 1 by dotted lines) was 2.22. The W:L ratio of the 17 arteries in noninflammatory tissue (solid lines) was 1.39. It is postulated

that the slightly greater ratio in the arteries in the inflammatory areas may have been due to decrease in size of the lumina of the vessels by external pressure caused by the exudate, but the difference between the inflammatory and noninflammatory areas does not seem to be of great significance. The average W:L ratio of all 24 arteries was 1.60 (over nine times that in the control cats).

On gross and microscopic examination there were no changes in the thyroid, parathyroid, liver, pancreas, spleen, adrenal, kidneys, bladder,



Text-Fig. 1. The external diameter of each artery is plotted on the ordinates, the ratio of the wall to the lumen (W:L) on the abscissas. The vessels in inflammatory areas (cat 2) are indicated by dotted lines, those in noninflammatory areas by solid lines.

reproductive organs, pituitary body, brain, or bone marrow. There were lipochrome deposits at the nuclear poles of the myocardial cells, and slight scarring and thickening of the basement membrane of the glomeruli, but there were conspicuously few changes attributable to senility, as compared to what would be expected in men of corresponding age.

Thirty-five arteries from organs other than the lungs were measured and showed no variations from organ to organ. In only 3 arteries, each less than 80 μ in external diameter, was the W:L ratio over 0.4, the greatest ratio being 0.585. The average W:L ratio of the 35 arteries was 0.164, almost exactly one-tenth of that in the pulmonary arteries of this cat.

Cat 3

Cat 3 was a large male cat weighing 4.59 kg., with an unknown past history. It died following the same type of experiment as that for which cat 1 was used. Thickening of the pulmonary arteries was less advanced than in cats 1 and 2, but was significant. The measurements have been charted. The average W:L ratio was 0.57 (over three times the ratio found in controls).

Injection of Pulmonary Arteries in Cats 4 to 7, Inclusive

We hoped by injection to study the distensibility of hyperplastic arteries. Unfortunately, the arteries of four cats injected were entirely normal, so that we obtained no knowledge of the behavior of hyperplastic vessels with this procedure. We injected the pulmonary arteries of two lobes of each cat with lead-gelatin at about 40° C. and then chilled the tissues, using the adaptation by Dock [5] of the method of injection devised for the coronary arteries by Schlesinger.[6] One of the two lobes injected in each instance had been previously distended by intratracheal pressure, while the pulmonary artery of the other was injected when the lobe was collapsed. Other tissue from the same pairs of lungs was studied without arterial injection, sometimes with, sometimes without previous pulmonary distention. The injected arteries, as would be expected, had very low W:L ratios, the average of the 24 measured being 0.026. The average W:L ratio of 14 uninjected arteries of these four cats was 0.17. The latter are charted with the other control cats (Text-Fig. 1).

Control Cats

Slides were examined of tissue from the lungs of five additional cats (nos. 8, 9, 10, 11, and 12). In one (no. 11), no measurable arteries were found. Measurements of the other four are combined in Text-Figure 1, with those from the uninjected arteries of cats 4, 5, 6, and 7. The W:L ratio for 24 arteries from the eight cats was 0.17.

In a recent *human* autopsy (no. 11488) the pulmonary arteries and arterioles appeared to be much thicker than usual when examined without measurement. However, the W:L ratio of these vessels was only 0.13.

Discussion

It will be seen that the thickness of the pulmonary arteries as expressed by the W:L ratio had a different order of magnitude in cats 1 (1.36), 2 (1.60), and 3 (0.57) than in the remaining animals (0.17); also, that the W:L ratios of the extrapulmonary arteries in cat 2 (0.16) were much like those found in normal pulmonary arteries. In other words, in this animal at least, the changes were limited to the arteries in the lungs. The fact that all of the arteries in the sections studied were equally hyperplastic apparently shows that there was no beading of the arteries, as described by Ettinger [2] in the guinea-pig. Ettinger perfused the pulmonary artery of half-grown cats with Janus green, and found that there was enough constriction to reduce the perfusion rate by about 25 per cent. In a full-grown cat the constriction was enough to block the flow almost completely. The lung was sectioned immediately, and showed obliteration of the lumen of a pulmonary artery about 200 μ in external diameter. He interpreted the thickening of the arterial walls as due to the contraction of the vessel. Of the contraction there can be no doubt, but the enormous amount of smooth muscle shown in his illustrations must raise the question whether the constricted artery had not been extremely hyperplastic even before the perfusion. The picture in many ways resembles those found in our cats 1, 2, and 3, except that we did not find any separate bundles of longitudinal muscle in the adventitia of any of our animals. Wilens and Sproul [7] studied 487 rats kept over their entire natural life span. There were no constant morphologic changes with increasing age except in the coronary and pulmonary arteries. In the pulmonary arteries of almost every rat over 2 years of age there were degenerative changes, commonly with calcium deposition. They found "atrophy of the smooth muscle coat and replacement of fibrous tissue leading to irregular thickening of the wall. In less involved areas the smooth muscle often appeared hyperplastic." Smooth muscle hypertrophy in the media of a pulmonary artery is shown in their Figure 12. It resembles strongly that found in our cats 1, 2, and 3.

In the pulmonary arteries of our cats we found no lesions that we interpreted as atrophy. The smooth muscle cells were greatly enlarged and apparently increased in number. We interpret the picture as representing both hypertrophy and hyperplasia. There is no clear evidence in the animals studied that inflammation entered into the causation of the lesions. In the one case in which it was studied the heart was ap-

parently normal. On the other hand, although the muscle cells appeared large, there was no mitotic activity or other evidence of neoplasia. In other words, the cause of the process is entirely unknown.

The arterial change which we have described is apparently entirely unrelated to arteriosclerosis. Most reports on spontaneous arteriosclerosis in laboratory animals have dealt especially with changes in the aorta. However, Hueper [8] found cone-shaped calcified foci in the large and medium-sized branches of the pulmonary arteries in 12 of 75 rats examined. He considered these to be spontaneous. No lesions were found in the heart, aorta, liver, spleen, pancreas, adrenals, kidneys, or brain. In view of the experience of Hueper with degenerative lesions, and of Ettinger,[1,2] Wilens and Sproul,[7] and ourselves with the apparently very different hyperplastic changes, the possibility must be considered in the rat and cat that the preponderance of lesions in the pulmonary arteries may perhaps be related to the dependent position of the lungs in these animals. This possibility cannot be either established or denied with the data available.

Summary

In a very small percentage of cats, the pulmonary arteries show extreme hypertrophy and hyperplasia of the smooth muscle of the media. The cause of this lesion is unknown.

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DESCRIPTION OF PLATE

Plate 161

Fig. 1. Section of lung of cat 1. Nodular and confluent groups of arteries with marked hypertrophy of their walls. Hematoxylin and eosin stain. × 11.5.

Fig. 2. The group of vessels below and to the right of the center of Figure 1 is shown at a higher magnification. The extreme hypertrophy of the arterial walls is limited to the media, and depends upon hypertrophy and hyperplasia of smooth muscle. Hematoxylin and eosin stain. × 140.

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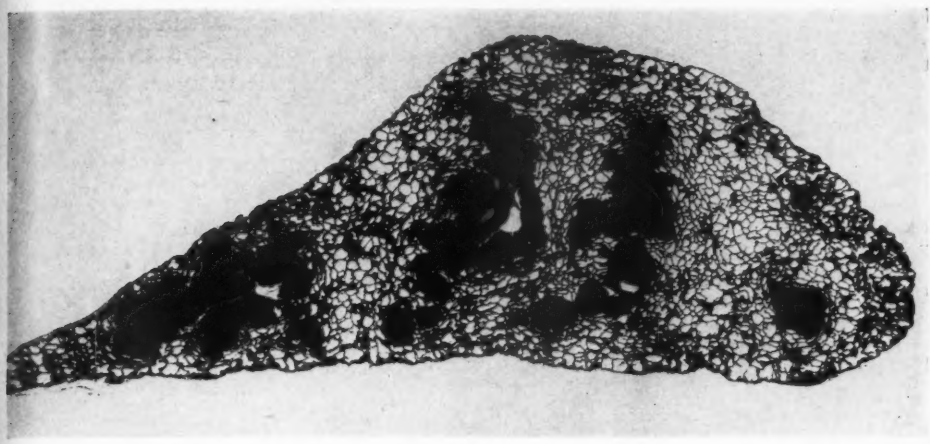

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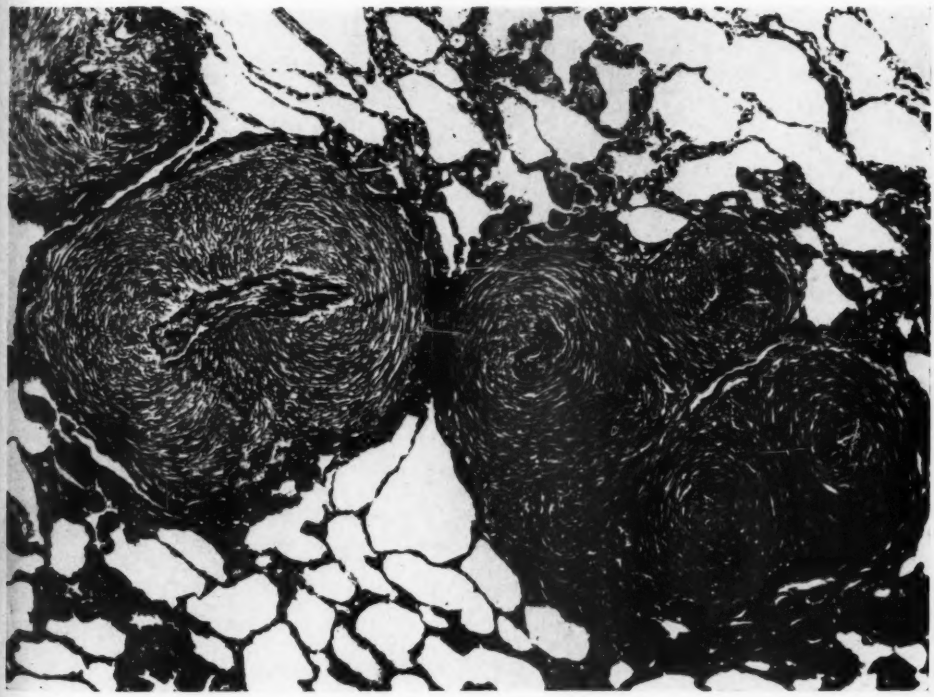

2

Olcott, Saxton, and Modell Medial Hyperplasia in Pulmonary Arteries

CEPHALOTHORACOPAGUS MONOSYMMETROS

Report of a Case *

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Double human monsters occur so infrequently that statistics on their incidence are not particularly accurate. It is estimated that they occur once in about 50,000 births.[1] One of the more common forms of equal conjoined twins are the cephalothoracopagi, in which certain parts of the head, neck, thorax, and abdomen are shared. Following is a description of such a monstrosity.

Report of Case

This monster was stillborn on March 6, 1945. Its mother was a white woman, 30 years old, who had had one previous pregnancy terminating in miscarriage at 11 weeks. The labor was difficult, lasting 25 hours. The vertex presentation was extracted manually. About 5 liters of amniotic fluid escaped during delivery. Birth occurred 4 weeks before the expected date of confinement. The mother was Rh positive.

Description

The monster consisted of two female babies "joined" ventrally from the midportion of the abdomen upward (Figs. 1 and 2). It measured 36 cm. in length. It presented one head, one neck, one chest, and one upper abdomen formed by a fusion of two, two lower abdomens, two pelves, four arms, and four legs.

Head. The relatively large head had two faces. The faces were situated approximately at right angles to one another. It is convenient to speak of the aspect of the monster presenting the faces as the anterior aspect. There were apparently three eyes. The lateral eyes were normal, but the middle eye was common to the two faces and protruded about half way from its socket. This double eye was really two single eyes, except for a circular defect in the sclera where the two eyes were joined. There were two corneas which were 5 mm. apart. At the scleral defect the two retinas were in contact with one another.

Each face had a nose and a mouth and there were no malformations of the lips or palates. There were two ears, one located on the lateral aspect of each face.

The head was anencephalic. At the vertex there was a circular defect of the scalp and skull measuring about 5 cm. across. Through this a mass of friable, dark reddish tissue protruded. Similar tissue filled the small cranial cavity. Microscopically this consisted of highly vascular

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disorganized neuroglia. There was a prominent bony ridge extending along the floor of the calvarium from the sella turcica to the occipital protuberance. This divided the posterior cranial fossa into right and left halves. A foramen magnum in the bottom of each half led into right and left spinal canals. Two optic nerves arose in the double eye and soon became lost in the amorphous material filling the skull.

Trunk and Extremities. From each foramen magnum extended a vertebral column (Fig. 3). The neck was short and thick. The common chest was large, consisting of a part of the chest of each twin. The chests were joined by the ribs and no sterna were present. The posterior rib segments were shorter than the anterior ones; thus the anterior shoulders were 11 cm. apart and the posterior shoulders were only 3.5 cm. apart. Each anterior shoulder possessed a clavicle, but the posterior shoulders had none. The anterior chest showed two nipples; no nipples were seen posteriorly.

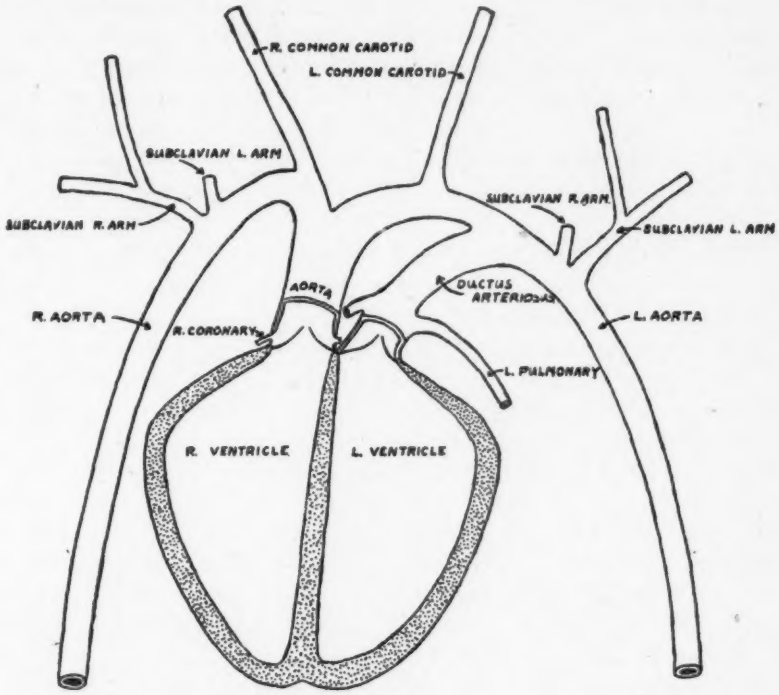
The abdomens were joined above the navel, but separate below. The navel and umbilical cord were single. The lower portion of each abdomen and the pelves appeared normal. Each twin had normally developed female external genitalia.

Body Cavities. The thorax contained one pericardial sac and two pleural cavities, one heart, and two lungs. The thorax and abdomen were separated by a single broad diaphragm. The abdominal organs consisted of one liver, one spleen, one stomach, one duodenum, two intestinal tracts, four adrenals, two complete urinary tracts, and two complete sets of female genitalia. The peritoneal cavities of the twins communicated above the umbilicus. There was a single lesser peritoneal sac behind the stomach.

Cardiovascular System. The heart was large and was located in the midline. The apex was deviated slightly to the right and showed a slight cleft where the right and left ventricles joined. The heart measured 4 cm. transversely, 4.5 cm. vertically, and 2 cm. anteroposteriorly. It had two auricles and two ventricles. The interventricular septum was intact. The interauricular septum was imperfect so that the auricles communicated with each other through a large foramen. The valves between the auricles and ventricles appeared normal.

The great vessels were transposed (Text-Fig. 1). The aorta arose from the right ventricle and the pulmonary trunk from the left ventricle. From the posterior part of the pulmonary trunk arose right and left pulmonary arteries; these vessels were small. The main part of the pulmonary trunk continued upward and to the left as the ductus arteriosus, and joined the left aorta between the left common carotid and subclavian arteries.

Right and left coronary arteries arose from the base of the aorta. The aortic trunk divided about 1 cm. above the heart into right and left aortas. From the left aorta arose the left common carotid artery and two subclavian arteries, one to each arm of the left twin. From the right aorta arose the right common carotid artery and two subclavian arteries, one to each arm of the right twin. Each descending aorta bore



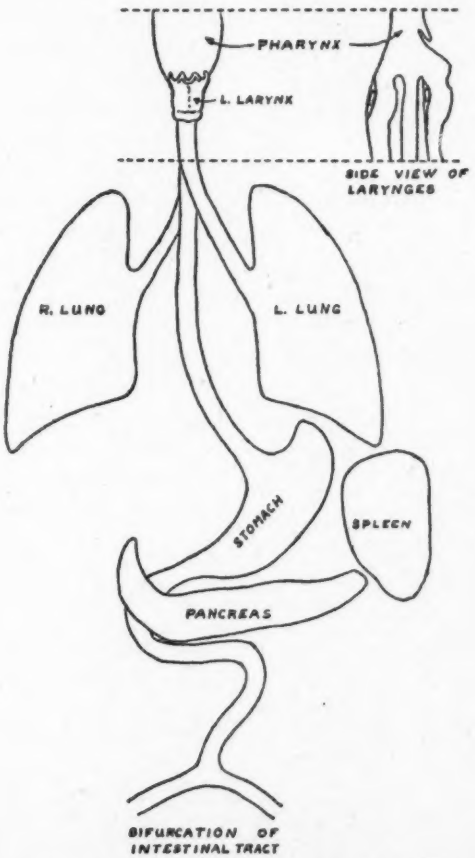
Text-Fig. 1. Arterial system.

the usual relationship to the respective spinal column, and the lower arterial system for each twin was normal.

There were two inferior venae cavae which joined just below the liver. The large vena cava thus formed entered the heart at the junction of the two auricles posteriorly. Right and left pulmonary veins entered the left auricle. A single superior vena cava entered the upper part of the right auricle. This vessel was formed by the junction of right and left innominate veins. Each innominate vein received an internal jugular and two subclavian veins. A right azygos vein also emptied into the right auricle posteriorly.

The single umbilical cord contained one large vein and two pairs of arteries. The vein entered the anterior surface of the liver and continued into the common vena cava. A pair of umbilical arteries passed in the proper location to each twin.

Respiratory System. The structures concerned with respiration consisted of the two noses, a Y-shaped pharynx, two larynges, two tracheae, and two lungs. The upper limbs of the Y-shaped pharynx communicated with the noses. The limbs met in the lower part of the oral pharynx and the hypopharynx continued as a single esophagus and as two larynges. One larynx was located anterior to the esophagus and the other was posterior to it. Each larynx faced anteriorly, thus making the relations of the posterior larynx to the pharynx and esophagus rather peculiar (Text-Fig. 2). There was one hyoid bone, and only one



Text-Fig. 2. Respiratory and gastrointestinal systems.

thyroid gland was found. The trachea from the anterior larynx continued without bifurcation into the left lung, and that from the posterior larynx led to the right lung.

The left lung was smaller than the right. It had two principal lobes, each of which showed rudimentary fissures. The right lung was large and very irregular in shape. It had five lobes.

The posterior part of the mediastinum consisted simply of a thin septum formed by right and left parietal pleurae. The posterior margin of this septum joined the posterior thoracic wall about midway between the posterior rib junction and the left spinal column. The anterior part of the septum contained the esophagus and joined the pericardium about in the midline.

Gastrointestinal System. There were one esophagus, one stomach, and one duodenum. All of these were relatively normal in position when viewed from the front, but they did not bear their usual relationship to a spinal column. About 15 cm. distal to the duodenum the jejunum bifurcated, and beyond this there were two intestinal tracts, each consisting of a portion of small intestine, an appendix, and a colon. Each colon was located entirely in the lower abdomen and did not follow the usual course.

Spleen. There was a single spleen located in the upper part of the abdomen. It was rotated so that the diaphragmatic surface faced forward and inward. The artery which supplied it arose from the left aorta.

Liver. There was a single, large liver located in the midline in the upper abdominal cavity, but it extended to the umbilicus. Viewed anteriorly the liver was roughly triangular with apex downward and the right and left halves symmetrical. There were two transverse fissures across the lower half of the anterior surface and a vertical fissure from the apex to the upper transverse fissure. The umbilical vein entered through this vertical fissure just below the upper transverse fissure. The vertical fissure continued on the posterior surface, and from it the common bile duct left the liver about 2.5 cm. from the apex to enter the duodenum. No gallbladder was found. The liver measured 7.5 by 7 by 3 cm. Posteriorly there was a large caudate lobe measuring 3 by 3 by 1.5 cm. The inferior vena cava passed through the liver just anterior to the caudate lobe.

Pancreas. There was a single pancreas in the usual location. A small piece of pancreatic tissue extended anteriorly and to the right of the duodenum.

Urinary Tracts. Each twin had a complete urinary tract, so that there were four kidneys, four ureters, and two bladders. The kidneys were normal in size, shape, and position.

Genitalia. Each twin had complete female genitalia. The ovaries, tubes, uteri, and vaginae were normal.

Nervous System. No abnormalities were observed in the peripheral nerves. There were four sympathetic chains, one on each side of each vertebral column.

Comment and Comparison

Obviously, conjoined twins are monozygotic. It is probable that monsters of this type occur when two primitive streaks forming on the ectodermal plate of a single developing ovum are in such close proximity in their cephalic and mid-portions that certain tissues subsequently developing from them are shared. In man, female double monsters are two or three times as frequent as males, although monozygotic male twins occur a little more frequently than females.[1]

Medical literature contains numerous descriptions of double monsters. A few similarities and differences between this case and others are recorded in the following paragraphs. A more extensive search would surely reveal cases even more closely resembling this one.

Cosmettatos [2] described a monster in which the head was anencephalic and presented two faces at right angles to one another. There were three eyes. The median eye possessed a single cornea and two optic nerves. Section revealed a scleral septum dividing the structure in two parts, each of which contained a retina and a lens. The body of this monster was essentially single although there were two vertebral columns as far as the sacrum.

A monster reported by Finola [3] had a single head with one face, but the external appearance of the double body closely resembled the case reported here. However, dissection revealed two complete sets of apparently normal thoracic organs. There was an arterial communication between the arches of the two aortas. The abdominal portion contained two sets of viscera, except for the gastrointestinal tract, which was single to a point 10 cm. proximal to the ileocecal valve where bifurcation occurred. A pancreas flanked each side of the duodenum, and the biliary tracts from the two livers emptied into opposite sides of the duodenum. Scammon [1] suggested that in monsters of this type the digestive tube is single to the level of the origin of the yolk stalk from the small intestine, and double beyond.

In a case of two conjoined fetuses, occurring in a set of monozygotic triplets reported by Messinger and Shryock,[4] the union occurred at the thorax and upper abdomen. The heart was a single four-chambered structure, and the umbilical cord contained two arteries and two veins. The livers were fused and cystic. The upper portion of the gut was

single and the lower portion was double. There was incomplete rotation and fixation of the colon with transposition of the colon in one fetus.

According to Jordan and Kindred,[5] the viscera in conjoined twins are frequently arranged in mirror image fashion. When this occurs it is always the right hand twin that shows the situs inversus viscerum. In the present case the fixation of the colons was so faulty that it was not possible to determine whether one was transposed.

In a double ovine monster described by Goss and Cole [6] the heart and great vessels were quite similar to those structures in the monster reported here. However, the great vessels were not transposed, and the right pulmonary artery arose from the right aorta instead of from the pulmonary trunk.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 162

FIG. 1. Anterior view of cephalothoracopagus monosymmetros.

FIG. 2. Posterior view of cephalothoracopagus monosymmetros.

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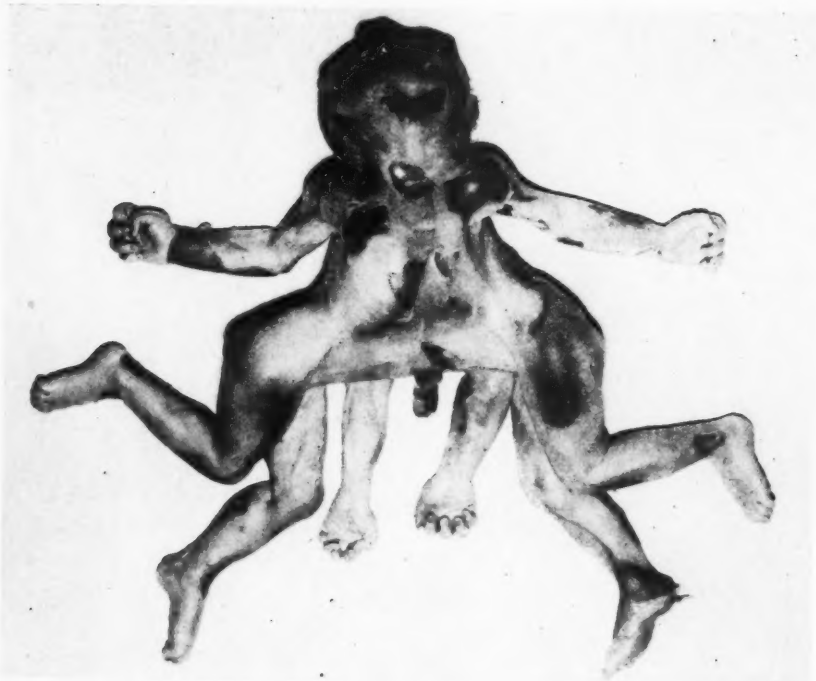

2

Gunter Cephalothoracopagus Monosymmetros

PLATE 163

FIG. 3. Roentgenogram of the cephalothoracopagus monosymmetros illustrated in the preceding figures.

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Gunter Cephalothoracopagus Monosymmetros